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(54) Title: MODULATION OF PEROXISOME PROLIFERATOR ACTIVATED RECEPTORS ACTIVITY

(57) Abstract: The present invention relates to compounds, compositions and methods useful for modulating nuclear receptors activity in cells, and for treating and/or preventing various diseases and conditions mediated by said nuclear receptors, including metabolic or cell proliferative disorders. According to particular aspects, the present invention relates to compounds, compositions and methods useful for modulating activities of the Peroxisome Proliferator Activated Receptors (PPARs) and for treating and/or preventing various diseases and conditions mediated by said nuclear receptors. More specifically, it relates to Peroxisome Proliferator Activated Receptor-gamma (PPAR-gamma) ligands, which are useful in the modulation of blood glucose levels and in the increase of insulin sensitivity in patients in need thereof. The properties of the compounds and compositions of the invention make these PPAR ligands particularly useful in the treatment of those diseases and conditions including diabetes, atherosclerosis, hyperglycemia, dyslipidemia, obesity, syndrome X, insulin resistance, hypertension, neuropathy, microvascular diseases (e.g. retinopathy, nephropathy), macrovascular diseases (e.g. myocardial infarction, stroke, heart failure) in mammals.

MODULATION OF PEROXISOME PROLIFERATOR ACTIVATED RECEPTORS ACTIVITY

The present invention relates to compounds, compositions and methods useful for modulating nuclear receptors activity in cells, and for treating and/or preventing various diseases and conditions mediated by said nuclear receptors, including metabolic or cell proliferative disorders. According to particular aspects, the present invention relates to compounds, compositions and methods useful for modulating activities of the Peroxisome Proliferator Activated Receptors (PPARs) and for treating and/or preventing various diseases and conditions mediated by said nuclear receptors. More specifically, it relates to Peroxisome Proliferator Activated Receptor-gamma (PPAR-gamma) ligands, which are useful in the modulation of blood glucose levels and in the increase of insulin sensitivity in patients in need thereof. The properties of the compounds and compositions of the invention make these PPAR ligands particularly useful in the treatment of those diseases and conditions including diabetes, atherosclerosis, hyperglycemia, dyslipidemia, obesity, syndrome X, insulin resistance, hypertension, neuropathy, microvascular diseases (e.g. retinopathy, nephropathy), macrovascular diseases (e.g. myocardial infarction, stroke, heart failure) in mammals.

The following description is provided to aid in understanding the invention but is not admitted to be prior art to the invention.

Diabetes mellitus refers to a disease process derived from multiple causative factors and characterized by elevated levels of glucose in blood, or hyperglycemia. Uncontrolled hyperglycemia is associated with increased and premature morbidity and mortality mainly due to an increased risk for microvascular and macrovascular diseases. Therefore, control of glucose homeostasis is a critically important approach for the treatment of diabetes.

At least two types of diabetes mellitus have been identified : (i) the Type I diabetes, or Insulin Dependent Diabetes Mellitus (IDDM), which is the result of a complete lack of insulin, the hormone that regulates glucose utilization under normal physiological conditions, and (ii) the Type II diabetes, or Non Insulin Dependent Diabetes Mellitus (NIDDM), which is due to a resistance to insulin stimulatory or regulatory effects on glucose and lipid metabolism in the main insulin-sensitive tissues, i.e. skeletal muscle, liver and adipose tissue. Said resistance to insulin responsiveness in Type II diabetes results in insufficient insulin activation of glucose uptake, oxidation and storage in muscle and inadequate insulin repression of lipolysis in adipose tissue and of glucose production and secretion in liver leading, directly or indirectly, to diseases and conditions such as atherosclerosis, hyperglycemia, dyslipidemia, obesity, syndrome X, insulin resistance, hypertension, neuropathy, microvascular diseases (e.g. retinopathy, nephropathy), macrovascular diseases (e.g. myocardial infarction, stroke, heart failure). In addition, it has been shown that excess body weight is directly associated with risk of cancer at several organ sites, including colon, breast (in postmenopausal women), endometrium, oesophagus, and kidney (Bianchini et al., 2002, Lancet Oncol., 3, 565-574). Type II or Non-Insulin Dependent Diabetes Mellitus (Type II

diabetes) constitutes 90 to 95% of all diabetic cases, and about 90% of these people are obese.

The primary aim of treatment for both forms of diabetes mellitus (DM) is the same, namely, the reduction of blood glucose levels to as near normal as possible. Treatment of Type I diabetes involves administration of replacement doses of insulin, generally by the parenteral route. In contrast, treatment of Type II diabetes does not require administration of insulin. Initially, treatments have been proposed which were based on diet and lifestyle changes augmented by therapy with oral hypoglycemic agents. However, while physical exercise and reductions in dietary intake of calories can improve the diabetic condition, compliance with this treatment is very poor because of sedentary lifestyles and excess food consumption, especially high fat containing food. Additionally, treatment with oral hypoglycemic agents such as sulfonylurea (e.g. tolbutamide, glipizide) derivatives, which stimulate the pancreatic cells to secrete more insulin, may lead to major adverse effects such as hypoglycemic reactions, including coma, which are highly unpredictable and prejudicial.

Thus, new class of drugs for the treatment of type II diabetes have been developed, i.e. thiazolidinediones or TZDs (glitazones), which act by improving insulin sensitivity in adipose tissue, liver and muscle. Treatments with said agents have been tested in several animal models of type II diabetes and resulted in complete correction of the elevated plasma levels of glucose, triglycerides and nonesterified free fatty acids without any occurrence of hypoglycemic reactions (Cheng Lai and Levine, 2000, Heart Dis., 2, 326-333). Examples of these thiazolidinediones are rosiglitazone, pioglitazone and troglitazone. However, while offering attractive therapeutic effects, these compounds suffer from numerous serious undesirable side effects including hemodilution (including oedema), liver toxicity, body weight increase (including body

fat increase, plasma volume increase, cardiac hypertrophy, increase of the adipocyte differentiation leading to increase obesity), modest but significant LDL-chol increase, anaemia (for a review, see Lebovitz, 2002, Diabetes Metab. Res. Rev., 18, Suppl 2, S23-9).

It has been shown that thiazolidinediones exert their effects by binding to specific nuclear receptors, and more specifically to Peroxisome Proliferator Activated Receptor (PPAR). It is furthermore recognized that they act as agonists of PPAR-gamma.

The nuclear receptors are activated by small lipophilic ligands and, in the activated state, function as transcription factors that can regulate the expression of genes involved in a broad range of developmental and physiological processes ranging from cell differentiation and development to lipid metabolism and energy homeostasis. They act by binding to DNA response elements (REs) within the promoter region of target genes and regulate transcriptional activation of said genes (for a review, see Escriva et al., 2000, BioEssays, 22, 717-727).

Peroxisome Proliferators Activated Receptors (PPARs) are transcription factors that belong to the nuclear hormone receptor superfamily. The PPARs function as ligand-activated transcription factors that control the expression of target genes by binding as heterodimers with the retinoid X receptors (RXRs) to cognate sequences (PPREs) in the promoter regions of their target genes. The first PPAR target genes identified were found to encode mainly enzymes involved in glucose, lipid, and cholesterol metabolisms. However, further investigations have shown that PPARs have pleiotropic biological activities and wide-ranging medical applications, extending from the treatment of metabolic disorders to possible applications in inflammation and cancer (Spiegelman,

1998, Diabetes, 47, 507-514 ; Schoonjans et al., 1997, Curr. Opin. Lipidol., 8, 159-166). Those skilled in the art will appreciate the numerous additional examples of PPAR mediated diseases and pathologic conditions that have been described in the literature. As indicated above, the discovery that these transcription factors are involved in the control of lipid metabolism has provided new insights into the regulation of vertebrate energy homeostasis, and further has provided new molecular targets for the development of therapeutic agents for disorders such as diabetes, obesity, dyslipidemia, cardiovascular disease and related conditions.

The PPAR subfamily includes three subtypes, i.e. PPAR-alpha, PPAR-beta and PPAR-gamma that have distinct tissue expression patterns and exert different physiological roles. PPAR-alpha (PPARα or NR1C1) is highly expressed in the liver, skeletal muscle, kidney and heart, and stimulates the expression of several enzymes involved in peroxisomal beta-oxidation. In addition to being activated by a variety of medium and long-chain fatty acids, PPAR-alpha was found to be the molecular target of the fibrate class of hypolipidemic drugs, such as clofibrate (i.e. 2-(4-chlorophenoxy)-2-methylpropanoic acid ethyl ester), fenofibrate (i.e. 2-(4-(4-chlorobenzoyl)phenoxy)-2-methylpropanoic acid isopropyl ester), bezafibrate (i.e. 2-(4-(4-chlorobenzoylaminoethyl)phenoxy)-2-methylpropanoic acid), ciprofibrate (i.e. 2-(4-(2,2-dichlorocyclopropyl)phenoxy)isobutyric acid) , beclofibrate and etofibrate, as well as gemfibrozil (i.e. 2-(2,4-dimethylphenoxypropyl)-2-methylpropanoic acid) (Fruchart, 2001, Am. J. Cardiol., 88, 24N-29N). Examples of PPAR-alpha ligands are provided in US 6,071,955.

PPAR-beta (PPARβ or NR1C2; also known as PPAR-delta, PPARδ, NUC-1 or FAAR) is ubiquitously expressed and its role in

mammalian physiology is still largely undefined. However, Oliver et al. (2001, Proc. Natl. Acad. Sci., 98, 5306-11) have recently demonstrated that PPAR-beta is implicated in the regulation of reverse cholesterol transport and Michalik et al. (2000, Horm. Res., 54, 263-268) have shown that PPAR-beta is implicated in the control of keratinocyte proliferation and is necessary for rapid healing of a skin wound. The human DNA sequences for the PPAR-beta has been cloned and is fully described in Schmidt et al., 1992, Molecular Endocrinology, 6, 1634-1641, and is herein incorporated by reference.

PPAR-gamma (PPARγ or NR1C3) is most abundantly expressed in adipose tissues, the large intestine, and cells of the monocyte lineage. PPAR-gamma plays a central role in adipogenesis, the regulation of fatty acid storage in adipose tissue, insulin sensitization and in the control of circulating glucose levels. PPAR-gamma has been reported to affect cell proliferation, differentiation (e.g. adipocyte differentiation) and apoptosis pathways. Further evidence is accumulating that suggests an important role for PPAR-gamma in atherosclerosis, inflammation and cancer (for a review, Fajas et al., 2001, J. Mol. Endo., 27, 1-9 or Rosen et al., 2000, Genes & Dev 14, 1293-1307, herein incorporated by reference). PPAR-gamma ligands include prostaglandins, fatty acids, N-(2-benzoylphenyl)tyrosine analogues, and the above disclosed thiazolidinediones (Lenhard, 2001, Receptors Channels , 7, 249-58). The DNA sequences for the PPAR-gamma receptors have been described in Elbrecht, et al., 1996, BBRC 224, 431-437, and are herein incorporated by reference (see also reference P37231 of NCBI data base). For a general review on PPAR-gamma, see Houseknecht et al., 2002, Domestic Animal Endocrinology, 22, 1-23 which is herein incorporated by reference in its entirety.

Literature provides numerous examples illustrating that PPARs are closely involved in a wide array of diseases or pathological conditions which are associated with cells expressing these nuclear receptors. More specifically, PPARs are useful as drug targets in methods for reducing blood glucose, cholesterol and triglyceride levels and are accordingly explored for the treatment and/or prophylaxis of insulin resistance (Type II diabetes ; see for example WO 98/05331), impaired glucose tolerance, dyslipidemia, and other disorders related to Syndrome X, also known as Metabolic Disease Syndrome, (WO 97/25042, WO 97/10813, WO 97/28149 ; see also Kaplan et al., 2001, J. Cardiovasc. Risk, 8, 211-7) including hypertension, obesity, atherosclerosis, thrombosis (Duez et al., 2001, J. Cardiovasc. Risk, 8, 185-186), coronary artery disease and other cardiovascular disorders. Further, PPARs have been shown to be potential targets for the treatment of inflammatory diseases such as cutaneous disorders (including acne vulgaris, cutaneous disorders with barrier dysfunction, cutaneous effects of aging, poor wound healing associated with altered signal transduction ; see Smith et al., 2001, J. Cutan. Med. Surg., 5, 231-43), gastrointestinal diseases (WO 98/43081) or renal diseases including glomerulonephritis, glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis ; similarly PPAR ligands should be useful for improving cognitive functions in neurologic diseases (Landreth and Heneka, 2001, Neurobiol. Aging, 22, 937-44) or in dementia, for treating diabetic complications, psoriasis, polycystic ovarian syndrome (PCOS) or for preventing and treating bone loss, e.g. osteoporosis ; or for antiviral, antiproliferative or antitumoral treatments (see for example US 5,981,586 or US 6,291,496).

Thus, the PPARs have been shown to be exciting targets for the development of therapeutic compounds likely to have utility at least in the treatment and/or prevention of

diseases that involve insulin sensitivity, lipid and glucose homeostasis, such as diabetes mellitus, as well as vascular or inflammatory diseases or disorders.

Although, as stated above, while the responses observed in the context of these various treating and/or preventing methods, are encouraging, they are not fully satisfactory treatments because of the occurrence of undesirable side effects (see above and Haskins et al., 2001, Arch Toxicol. , 75, 425-438 ; Yamamoto et al., 2001, Life Sci., 70, 471-482 ; Scheen, 2001, Diabetes Metab., 27, 305-313 ; Gale, 2001, Lancet, 357, 1870-1875 ; Forman et al., 2000, Ann. Intern. Med., 132, 118-121 or Al-Salman et al., 2000, Ann. Intern. Med., 132, 121-124). Thus, it is still desirable to have novel improved products and/or novel methods which enable the treatment and/or the prevention of diseases or conditions associated with cell types that express nuclear receptors, in particular the PPARs, and more specifically the PPAR-gamma.

The general problem underlying the invention is to develop new modulators of nuclear receptor activity, such as PPARs (and more specifically of PPAR-gamma). The Applicant has now identified compounds of general formula (I) below, their derivatives, their analogues, their pharmaceutically acceptable solvates or salts and pharmaceutical compositions containing them or mixtures thereof, which can be used for the treatment and/or prophylaxis of various diseases and conditions mediated or related to nuclear receptors, especially PPARs (and more specifically of PPAR-gamma), including metabolic or cell proliferative disorders such as, for example, diseases and conditions related to increased levels of lipids (e.g. hypertriglyceridemia and high levels of free fatty acids), hyperlipidemia, hyperinsulinemia, proliferation of the adipocytes, obesity, insulin resistance, insulin resistance leading to Type II diabetes and diabetic complications thereof (e.g. Syndrome X), hypertension,

atherosclerosis and coronary artery diseases. More specifically, said compounds and compositions are able to lower one or more of the following biological entities in patient: glucose, triglycerides, fatty acids, cholesterol, bile acid and the like, with better or equivalent efficacy and potency, but with lower toxicity and/or less undesirable side effects occurrence compared to known molecules in the art (e.g thiazolidinediones).

Another objective of the present invention is to provide compounds of the general formula (I) and their derivatives, their analogues, their pharmaceutically acceptable solvates or salts and pharmaceutical compositions containing them or mixtures thereof which have agonist activity against PPAR-gamma, and preferably partial agonist activity against PPAR-gamma.

Another objective of the present invention is to provide compounds of the general formula (I) and their derivatives, their analogues, their pharmaceutically acceptable solvates or salts and pharmaceutical compositions containing them or mixtures thereof having enhanced activities towards PPAR, especially PPAR gamma, without undesirable side effect or with limited undesirable side effect.

Yet another objective of the present invention is to provide a process for the preparation of compounds of the general formula (I) and their derivatives, their analogues, their pharmaceutically acceptable solvates or salts.

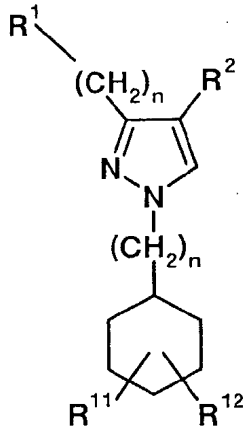
Still another objective of the present invention is to provide pharmaceutical compositions containing compounds of the general formula (I), their derivatives, their analogues, their pharmaceutically acceptable solvates or salts or their mixtures in combination with suitable carriers, solvents, diluents and other media normally employed in preparing such compositions.

Still another objective of the present invention is to provide methods of treatment and/or prophylaxis of various diseases and conditions mediated or related to nuclear receptors, especially PPARs (more specially PPAR-gamma), which use the compounds or compositions as the active ingredient.

Another objective of the present invention is to provide methods of treatment and/or prophylaxis as above mentioned resulting, in the treated patient, in enhanced beneficial effects (e.g. lowering blood glucose levels and/or improving insulin sensitivity in adipose tissue, liver and skeletal muscle) without toxic effect or with limited toxic effect and /or without undesirable side effect or with limited undesirable side effects.

Further objectives will become apparent from reading the following description.

According to a first embodiment, the present invention concerns compounds of the general formula (I):

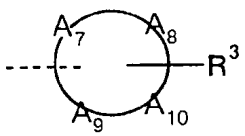


or analogues, derivatives, solvates or salts thereof,

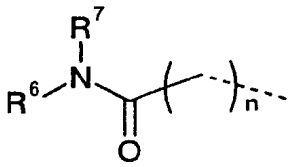
wherein :

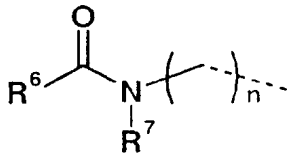
R^1 is a moiety selected in the group consisting of :

(i)

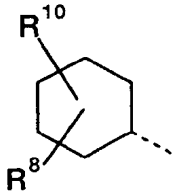


(ii)





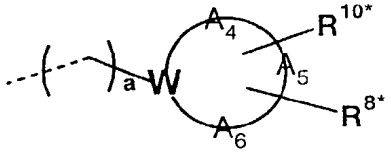
(iii)



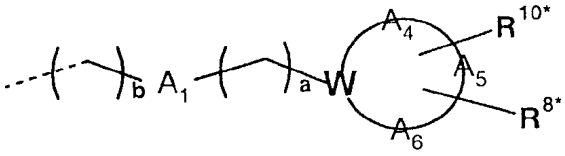
(iv) H, CF_3, $-(CH_2)_n-R^3$ and $-C_{n'}H_{2n'+1}$

R^2 is a moiety selected in the group consisting of :

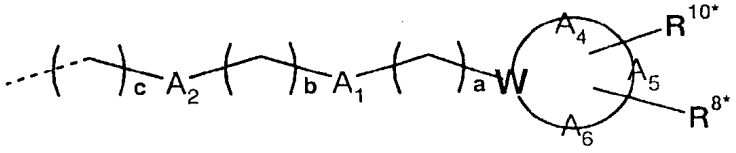
(i)



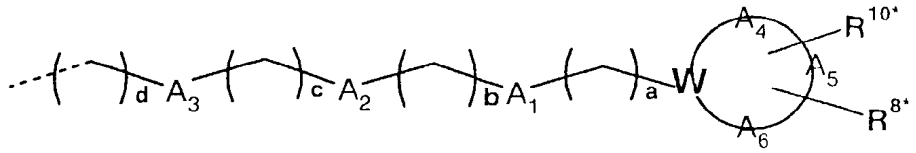
(ii)



(iii)



(iv)



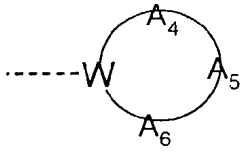
with :

X is a moiety selected in the group consisting of O and S ;

a, **b**, **c** and **d** are, independently from one another, an integer ranging from 0 to 4 ;

$\mathbf{A_1}$, $\mathbf{A_2}$ and $\mathbf{A_3}$ are, independently from one another, a moiety selected in the group consisting of - CO-, -O-, -CH-, $-CH_2-$, $-NR^9-$, and -CHOH- where R^9 is as above mentioned;

the moiety :



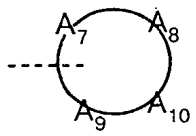
is intended to designate a mono or bi-cyclic carbo or hetero ring which can be unsaturated, or partially or completely saturated, containing 5-10 atoms;

W is an atom selected in the group consisting of C and N ;

$\mathbf{A_4}$, $\mathbf{A_5}$, $\mathbf{A_6}$ are, independently from one another, an atom selected in the group consisting of C, N, O and S ;

$\mathbf{A_7}$, $\mathbf{A_8}$, $\mathbf{A_9}$ and $\mathbf{A_{10}}$ are an atom selected in the group consisting of C, N, S and O ;

the moiety :



is intended to designate :

(i) a mono carbocyclic ring (i.e. a cyclic carboalkyl, with A_7, A_8, A_9 and A_{10} are C) ;

(ii) a mono heterocyclic ring (i.e. a cyclic heteroalkyl, with at least one A_7, A_8, A_9 and/or A_{10} is selected in the group consisting of N, S and O);

(iii) a bi- carbocyclic ring (i.e. a bicyclic carboalkyl with A_7, A_8, A_9 and A_{10} are C);

(iv) a bi- heterocyclic ring (i.e. a bicyclic heteroalkyl with at least one cyclic ring is containing at least one A_7, A_8, A_9 and/or A_{10} selected in the group consisting of N, S and O);

$\mathbf{R^3}$ is a moiety selected in the group consisting of H, a C_{1-4} alkyl moiety (esp. methyl), $-(CH_2)_n-CONR^{13}R^5$, $-CO_2R^4$, $-COR^4$ (esp. -CO-methyl or $-CONH_2$), $-OR^4$ (esp. -O-methyl), $-(CH_2)_n-CO_2R^4$, $-(CH_2)_n-COR^4$, $-(CH_2)_n-OR^4$, $-NR^{13}R^5$, $-(CH_2)_n-NR^{13}R^5$, $-NH-COR^4$, $-(CH_2)_n-NH-COR^4$, -Cl, -F, $-(CH_2)_nCO_2H$, $-O-(CH_2)_nCO_2H$, $-(CH_2)_n-TZD$, $-O-(CH_2)_n-TZD$, -CN, $-NO_2$, -OH, $-OCF_3$, $-COCF_3$, $-CF_3$, $-N(C_{n'}H_{2n'+1})_2$, $-SO_2-N(R^9)(R^{9*})$, $-NR^9-SO_2CF_3$, and $-NR^9-SO_2-C_{n'}H_{2n'+1}$ (e.g. $-NR^9-SO_2$butyl);

$\mathbf{R^4}$ is a moiety selected in the group consisting of H, $-C_{n'}H_{2n'+1}$ (e.g. C_{1-4} alkyl moiety such as methyl and ethyl), $-(CH_2)_nCO_2H$, $-NH_2$, $-(CH_2)_n-TZD$, -OH, $-N(C_{n'}H_{2n'+1})_2$, $-NR^9-SO_2CF_3$ and $-NR^9-SO_2-C_{n'}H_{2n'+1}$ (e.g. $-NR^9-SO_2$butyl);

$\mathbf{R^5}$ and $\mathbf{R^{13}}$ are, independently from one another, a moiety selected in the group consisting of H, a C_{1-4} alkyl

moiety (e.g. methyl and ethyl), $-SO_2CF_3$, and $-SO_2-C_{n'}H_{2n'+1}$ (e.g. SO_2butyl);

R^6 and R^7 are, independently from one another, a moiety selected in the group consisting of H, an alkyl, more specifically a C_{1-4} alkyl moiety, a C_6 cycloalkyl moiety (e.g. a cyclohexyl or a phenyl moiety), or a C_7 cycloalkyl moiety (e.g. a cycloheptyl or a benzyl moiety), $-SO_2CF_3$, $-SO_2-C_{n'}H_{2n'+1}$ (e.g. $-SO_2$Butyl), a benzyl moiety or phenyl moiety substituted at position 2 and/or 3 and/or 4 with a moiety selected in the group consisting of $-OC_{n'}H_{2n'+1}$, -Cl, -F, $-(CH_2)_nCO_2H$, $-O-(CH_2)_nCO_2H$, $-(CH_2)_n$-TZD, $-O-(CH_2)_n$-TZD, -CN, $-NO_2$, $-C_{n'}H_{2n'+1}$, $-CO-C_{n'}H_{2n'+1}$, $-SO_2-C_{n'}H_{2n'+1}$, $-NR^9-SO_2CF_3$, $-NR^9-SO_2-C_{n'}H_{2n'+1}$ (e.g. $-NR^9-SO_2$butyl), $-OCF_3$, $-COCF_3$, $-CF_3$;

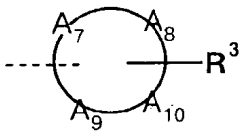
R^8 and R^{8*} are, independently from one another, a moiety selected in the group consisting of H, $-C_{n'}H_{2n'+1}$, a C_6 cycloalkyl moiety (e.g. a cyclohexyl or a phenyl moiety), $-OC_{n'}H_{2n'+1}$, -Cl, -F, $-(CH_2)_nCO_2H$, $-CF_3$, $-OCF_3$, $-COCF_3$, $-O-(CH_2)_nCO_2H$, $-(CH_2)_n$-TZD, $-O-(CH_2)_n$-TZD, $-CH-(CH_2)_n$, $-(CH_2)_n-N(R^9)(R^{9*})$, -CN, $-NO_2$, $-(CH_2)_n-CO-C_{n'}H_{2n'+1}$, $-(CH_2)_n-CO-N(R^9)(R^{9*})$, $-SO_2-N(R^9)(R^{9*})$, $-NR^9-SO_2CF_3$, $-(CH_2)_n$-CO-cycloalkyl (e.g. -CO-cyclohexyl or -CO-phenyl), $-O-(CH_2)_n$- cycloalkyl (e.g. $-O-(CH_2)_n$-cyclohexyl or $-O-(CH_2)_n$-phenyl), $-(CH_2)_n$-cycloalkyl (e.g. $-(CH_2)_n$-cyclohexyl or $-(CH_2)_n$-phenyl), $-NR^9-SO_2-C_{n'}H_{2n'+1}$ (e.g. $-NR^9-SO_2$butyl);

R^9 and R^{9*} are, independently from one another, a moiety selected in the group consisting of H, $-CO-C_{n'}H_{2n'+1}$, $-SO_2-C_{n'}H_{2n'+1}$, and a C_{1-4} alkyl moiety;

R^{10} and R^{10*} are, independently from one another, a moiety selected in the group consisting of H, an alkyl, more specifically a C_{1-4} alkyl moiety, a C_6

cycloalkyl moiety (e.g. a cyclohexyl or a phenyl moiety), or a C_7 cycloalkyl moiety (e.g. a cycloheptyl or a benzyl moiety),-Cl, $-OC_{n'}H_{2n'+1}$, - CF_3, $-OCF_3$, - $COCF_3$,-CN, $-NO_2$;

R^{11} and R^{12} is, independently from one another, a moiety selected in the group consisting of H, a C_{1-4} alkyl moiety, $-(CH_2)_n-CONR^{13}R^5$, $-CO_2R^4$, $-COR^4$, $-OR^4$, $-(CH_2)_n-CO_2R^4$, $-(CH_2)_n-COR^4$, $-(CH_2)_n-OR^4$, $-NR^{13}R^5$, $-(CH_2)_n-NR^{13}R^5$, $-NH-COR^4$, $-(CH_2)_n-NH-COR^4$, $-OC_{n'}H_{2n'+1}$, -Cl, -F, $-(CH_2)_nCO_2H$, $-O-(CH_2)_nCO_2H$, $-(CH_2)_n-TZD$, $-O-(CH_2)_n-TZD$, -CN, $-NO_2$, -OH, $-OCF_3$, $-COCF_3$, $-CF_3$, $-N(C_{n'}H_{2n'+1})_2$, $-SO_2-N(R^9)(R^{9*})$, $-NR^9-SO_2CF_3$, $-NR^9-SO_2-C_{n'}H_{2n'+1}$ (e.g. $-NR^9-SO_2$butyl), and :



;

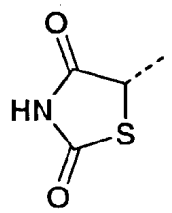
and

with in all the above :

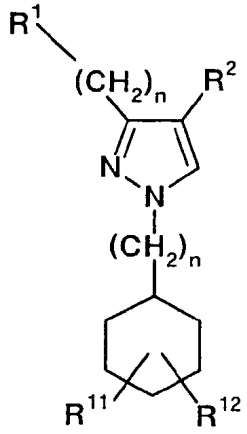
n is, independently from one another, an integer ranging from 0 to 6,

n' is, independently from one another, an integer ranging from 1 to 4, preferably from 1 to 3 and preferably from 1 to 2 ;

and TZD is :



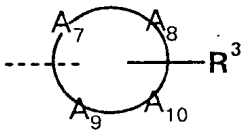
According to one special embodiment, the present invention concerns compounds of the general formula (I):



or analogues, derivatives, solvates or salts thereof,

wherein :

the R^1 moiety :



is intended to designate :

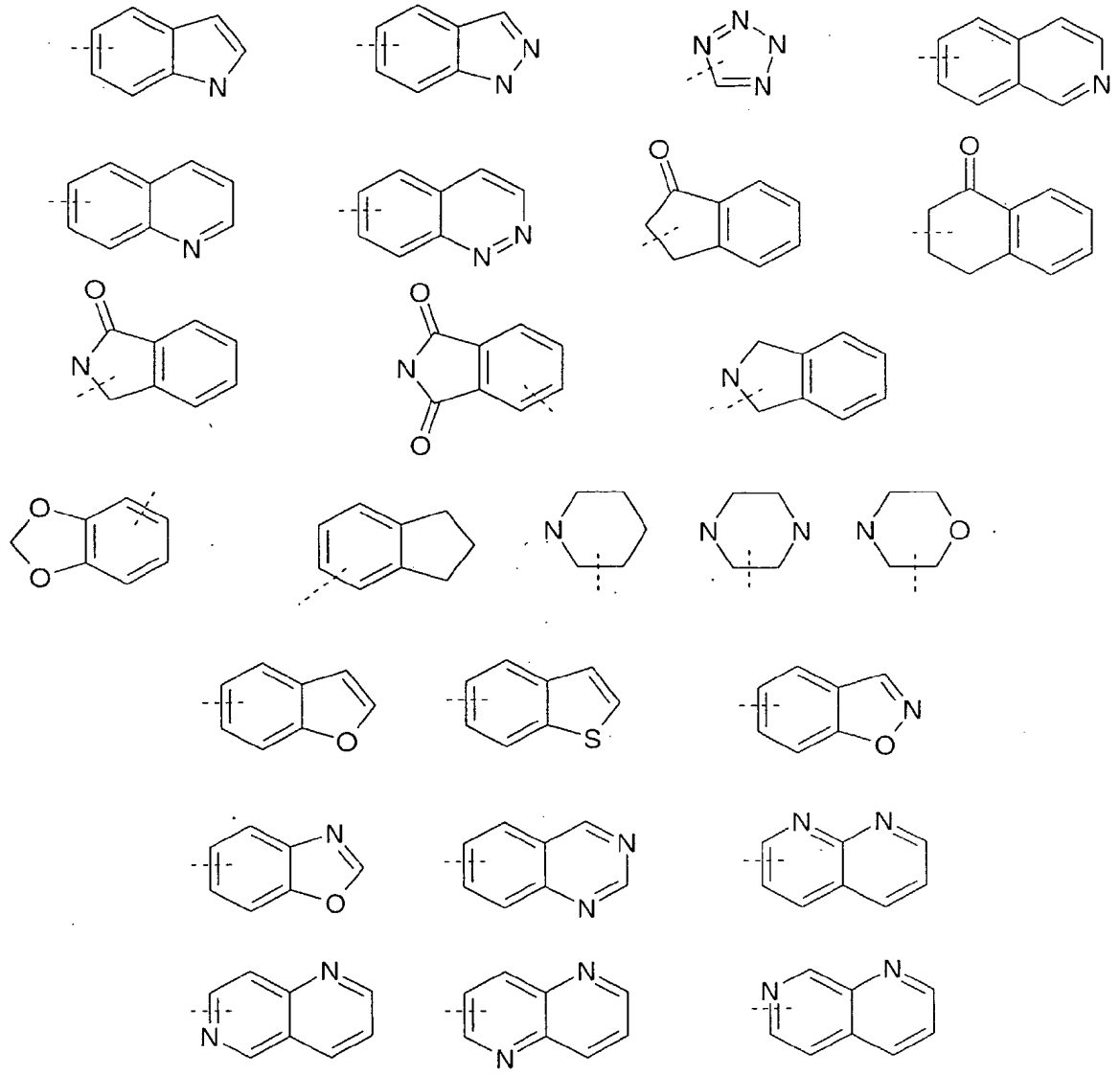
(i) a R^3 substituted mono carbocyclic ring (i.e. a cyclic carboalkyl, with A_7, A_8, A_9 and A_{10} are C) ;

(ii) a R^3 substituted mono heterocyclic ring (i.e. a cyclic heteroalkyl, with at least one A_7, A_8, A_9 and/or A_{10} is selected in the group consisting of N, S and O);

(iii) a R^3 substituted bi- carbocyclic ring (i.e. a bicyclic carboalkyl with A_7, A_8, A_9 and A_{10} are C);

(iv) a R^3 substituted bi- heterocyclic ring (i.e. a bicyclic heteroalkyl with at least one cyclic ring is containing at least one A_7, A_8, A_9 and/or A_{10} selected in the group consisting of N, S and O).

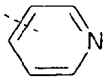
Additionally, said carbocyclic and/or heterocyclic ring (including both mono and bi) can be unsaturated, or partially or completely saturated, and is containing from 5 to 10 atoms. Examples of said carbocyclic and/or heterocyclic rings are :

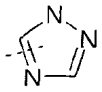



furane


thiophene

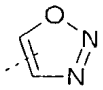

pyrrole


pyridine

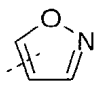

1,2,4-triazole


oxazole

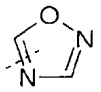

isothiazole

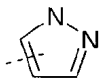

1,2,3-oxadiazole

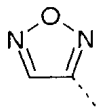

1,2,3-triazole

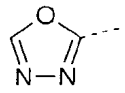

isoxazole

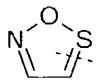

thiazole

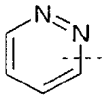

1,2,4-oxadiazole

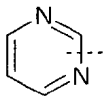

pyrazole

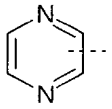

1,2,5-oxadiazole

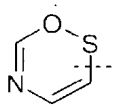

1,3,4-oxadiazole

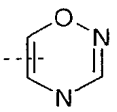

1,2,5-oxathiazole

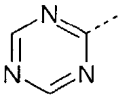

pyridazine

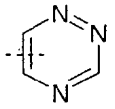

pyrimidine

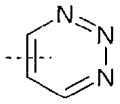

pyrazine

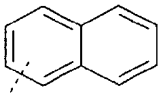

1,2,5-oxathiazine

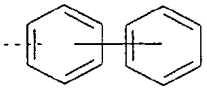



s-triazine

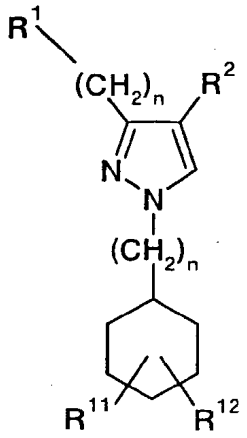

as-triazine


v-triazine





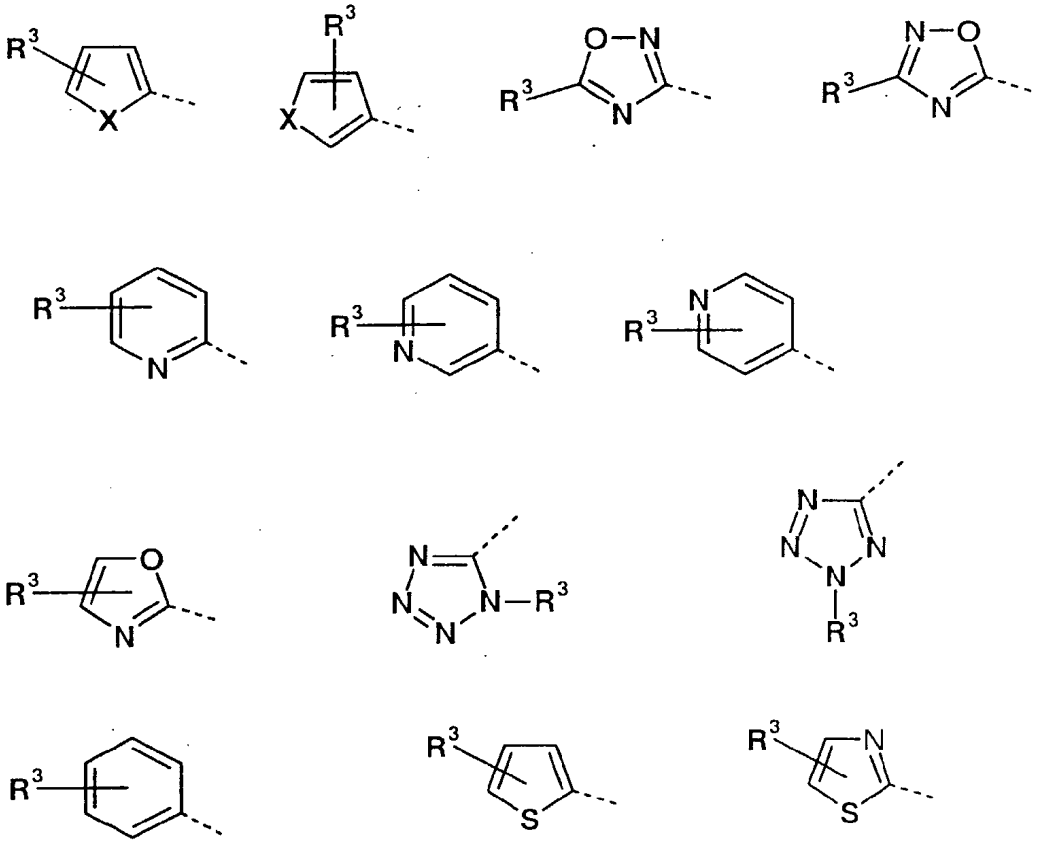
According to another special embodiment, the present invention concerns compounds of the general formula (I):



or analogues, derivatives, solvates or salts thereof,

wherein :

R^1 is a moiety selected in the group consisting of :

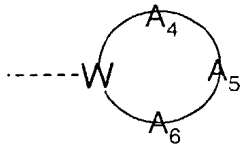


with X is a moiety selected in the group consisting of O, N and S ; and the other substituting moieties being as defined above.

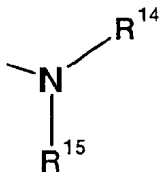
Alternatively, R^3 in R^1 is replaced with R^{11}.

According to one specific embodiment, the present invention concerns compounds of the general formula (I) wherein W is N and A_4, A_5, A_6 are C.

According to another specific embodiment, the present invention concerns compounds of the general formula (I) wherein the moiety :



is replaced with



wherein :

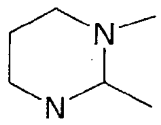
R^{14} is a moiety selected in the group consisting of H, an alkyl, $-C_{n'}H_{2n'+1}$,more specifically a C_{1-3} alkyl moiety, a C_6 cycloalkyl moiety (e.g. a cyclohexyl or a phenyl moiety), or a C_7 cycloalkyl moiety (e.g. a cycloheptyl or a benzyl moiety), $-CH-(CH_2)_n$,-CO-cycloalkyl (e.g. -CO-cyclohexyl or -CO-phenyl), $-(CH_2)_n$-cycloalkyl (e.g. $-(CH_2)_n$-cyclohexyl or $-(CH_2)_n$-phenyl), $-(CH_2)_nCO_2H$, $-(CH_2)_n$-TZD, -Cl, -F, $-(CH_2)_nCO_2H$, $-CF_3$, $-OCF_3$, $-O-(CH_2)_nCO_2H$, $-(CH_2)_n$-TZD, $-O-(CH_2)_n$-TZD, $-(CH_2)_n-N(R^9)(R^{9*})$, -CN, $-NO_2$, $-(CH_2)_n-CO-C_{n'}H_{2n'+1}$, $-(CH_2)_n-NH-CO-C_{n'}H_{2n'+1}$, $-(CH_2)_n-CO-NH-C_{n'}H_{2n'+1}$, $-(CH_2)_n-CO-N(R^9)(R^{9*})$, $-SO_2-N(R^9)(R^{9*})$, $-NR^9-SO_2CF_3$, $-(CH_2)_n$-CO-cycloalkyl (e.g. -CO-cyclohexyl or -CO-phenyl), $-O-(CH_2)_n$- cycloalkyl (e.g. $-O-(CH_2)_n$-cyclohexyl or $-O-(CH_2)_n$-phenyl), $-(CH_2)_n$-cycloalkyl (e.g. $-(CH_2)_n$-cyclohexyl or $-(CH_2)_n$-phenyl), $-NR^9-SO_2$butyl, and

R^{15} is a moiety selected in the group consisting of H, an alkyl, more specifically a C_{1-3} alkyl moiety, a C_6 cycloalkyl moiety (e.g. a cyclohexyl or a phenyl moiety), or a C_7

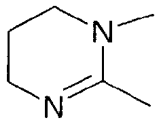
cycloalkyl moiety (e.g. a cycloheptyl or a benzyl moiety), -CO-cycloalkyl (e.g. -CO-cyclohexyl or -CO-phenyl), -$(CH_2)_n$-cycloalkyl (e.g. -$(CH_2)_n$-cyclohexyl or -$(CH_2)_n$-phenyl).

According to the present invention, the term "alkyl" as used herein, alone or in combination, is intended to designate a straight or branched chain, or cyclic carbon radical, or combination thereof, which may be fully saturated, mono- or polyunsaturated and can include di- and multi-moities. Typically, an alkyl moiety will have from 1 to 24 carbon atoms, with those moieties having 10 or fewer carbon atoms being preferred in the present invention. In rather preferred embodiment, the alkyl moieties of the invention are lower alkyl. A "lower alkyl" is a shorter alkyl chain having eight or fewer carbon atoms, preferably six or fewer carbon atoms, and even more preferably 4 or fewer carbon atoms (i.e. C_{1-4}). Typically, a C_{1-4} alkyl moiety according to the invention will have from 1 to 2 carbon atoms, with those moieties having 1 carbon atom being preferred in the present invention. Examples of saturated alkyl moieties include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl, (cyclohexyl)methyl, cyclopropylmethyl, n-pentyl, isopentyl, n-hexyl, isohexyl, n-heptyl, isoheptyl, n-octyl, and the like. An unsaturated alkyl moiety is one comprising one or more double bonds or triple bonds. Examples of unsaturated alkyl moieties include, but are not limited to, aromatic cycles such as for example phenyl and benzyl.

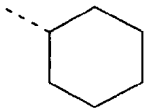
It should be understood that the cycles included in the compounds of the Invention can be fully or partially saturated or unsaturated. The skilled man can determine without undue experiment the localisation of the double /simple bonds. For example, an heterocycle :



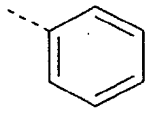
can be understood as being under the form of :



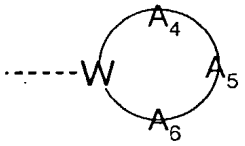
Similarly, the cycles designated with :



can be understood as being under an aromatic form :



According to special embodiments, the moiety :



is intended to designate :

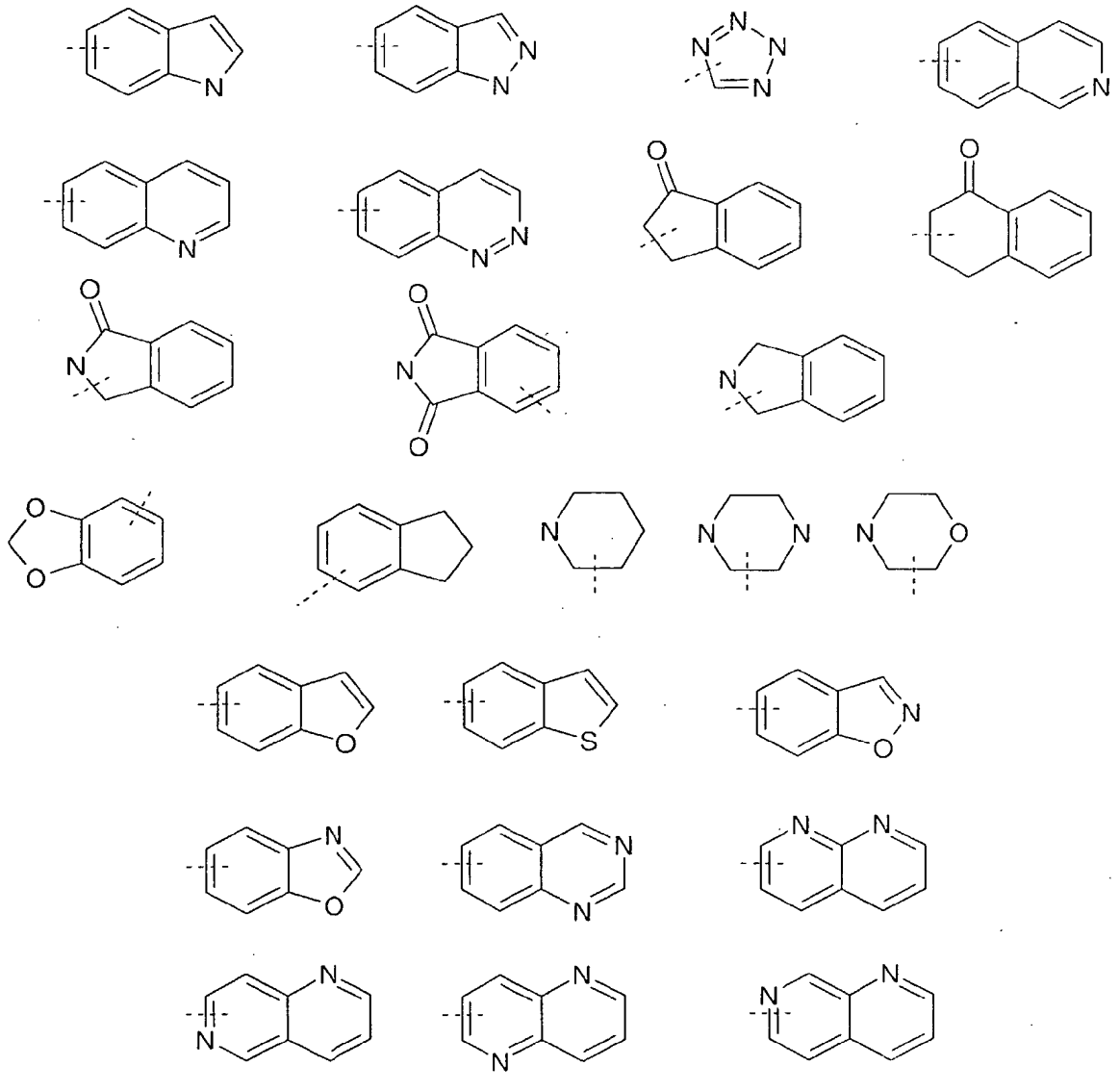
(v) a mono carbocyclic ring (i.e. a cyclic carboalkyl, with W, A_4, A_5 and A_6 are C)

(vi) a mono heterocyclic ring (i.e. a cyclic heteroalkyl, with at least one A_4, A_5, A_6 and/or W is as defined above and is not C)

(vii) a bi- carbocyclic ring (i.e. a bicyclic carboalkyl, with W, A_4, A_5 and A_6 are C)

(viii) a bi- heterocyclic ring (i.e. a bicyclic heteroalkyl with at least one A_4, A_5, A_6 and/or W is as defined above and is not C).

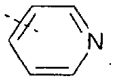
Additionally, said carbocyclic and/or heterocyclic ring (including both mono and bi - and including A_4, A_5 and A_6) can be unsaturated, or partially or completely saturated, and is containing from 5 to 10 atoms. Examples of said carbocyclic and/or heterocyclic rings are :



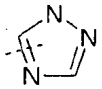
furane

thiophene

pyrrole

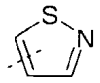


pyridine

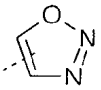


1,2,4-triazole

oxazole

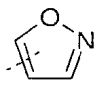


isothiazole



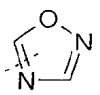
1,2,3-oxadiazole

1,2,3-triazole

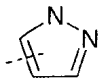


isoxazole

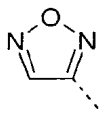
thiazole



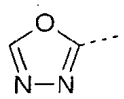
1,2,4-oxadiazole



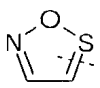
pyrazole



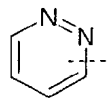
1,2,5-oxadiazole



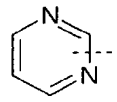
1,3,4-oxadiazole



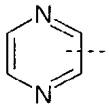
1,2,5-oxathiazole



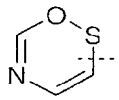
pyridazine



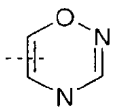
pyrimidine

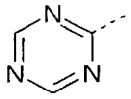


pyrazine

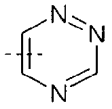


1,2,5-oxathiazine

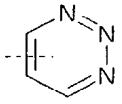




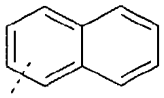
s-triazine

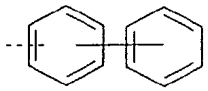


as-triazine

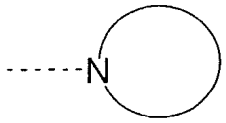


v-triazine





According to special embodiments, when W is N and A_4, A_5, A_6 are C, the moiety :



is intended to designate :

- a mono heterocyclic ring (i.e. a cyclic heteroalkyl)
- a bi- heterocyclic ring (i.e. a bicyclic heteroalkyl)

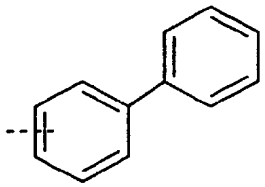
which can be unsaturated, or partially or completely saturated, containing 5-15 atoms. Alternatively, the heterocyclic ring can further contain at least one additional hetero atom (i.e. at least one A_4, A_5 or A_6 is not C) selected in the group consisting of N, S and O.

According to the present invention, the substituting moiety R present in a cycle (or cycloalkyl), for example an aromatic cycle, such as for example the followings :

can be localized in position para, meta and/or ortho of said cycle. In preferred embodiment, the substituting moiety is localized in position para or meta.

Additionally, the term "alkyl" is intended to further include those derivatives of alkyl comprising at least one heteroatom, selected from the group consisting of O, N and/or S (i.e. at least one carbon atom is replaced with one heteroatom). These alkyl derivatives are widely named "heteroalkyl" and as alkyl above described are intended to designate, by themselves or as part of another substituent, stable straight or branched chains, or cyclic moieties, or combinations thereof. According to specific embodiment, the nitrogen and sulfur atoms when present in the said heteroalkyl are further oxidized and/or the nitrogen heteroatom is quaternized. The heteroatom may be placed at any position of the heteroalkyl moiety, including the position at which the alkyl moiety is attached to the remainder of the molecule.

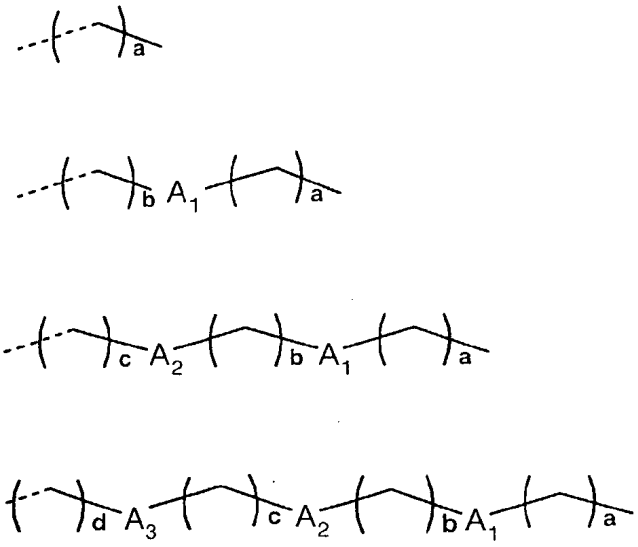
The terms "cycloalkyl" and "heterocycloalkyl", by themselves or as part of another substituent, are intended to designate cyclic versions of the above "alkyl" and "heteroalkyl", respectively. They include bicyclic, tricyclic and polycyclic versions thereof. According to one special embodiment, the term bicyclic (including both the carbo and hetero bicyclic) is intended to designate (i) the case where two cycles are fused together, e.g. naphthalene, or (ii) the case where one cycle is substituted with a second one, thereby forming a bicyclic structure, i.e. :



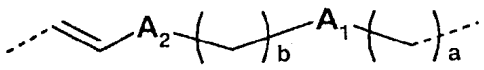
It should be noticed that the compounds of formula I are comprising several moieties which can be repeated n times (e.g. $-O-(CH_2)_nCO_2H$) ; it should be understood that each n value throughout the formula I in a particular compound can be chosen independently from one another. According to special embodiments of the invention, n is an integer ranging from 0 to 4, more particularly from 0 to 2, and preferably from 0 to 1. In preferred case it is 0.

According to the present invention, the term C_{1-4} alkyl is intended to designate a straight or branched chain, which may be fully saturated, mono- or polyunsaturated, having from 1 to 4 carbon atoms, such as methyl, ethyl, n-propyl, iso- propyl, and the like. Typically, a C_{1-4} alkyl moiety according to the invention will have from 1 to 2 carbon atoms, with those moieties having 1 carbon atom being preferred in the present invention. An unsaturated alkyl moiety is one comprising one or more double bonds or triple bonds.

According to special embodiments, at least one $-(CH_2)-$ moiety in the following structure (termed "linker") isolated from R^2:



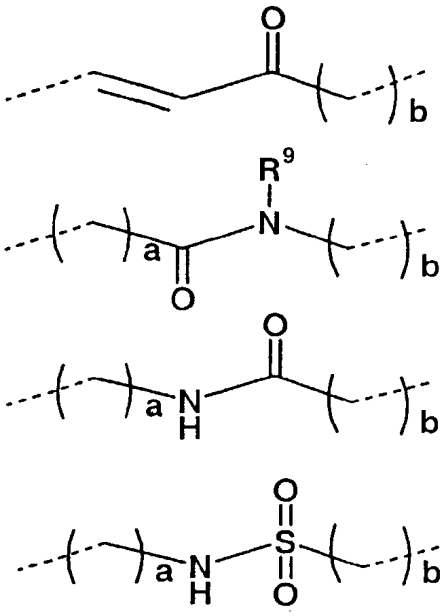
is replaced by at least one -(CH)- moiety. In this special case, those skilled in the art will be able to adapt the number and type of bounds accordingly. For example, said structure isolated from R^2 can be as follows :



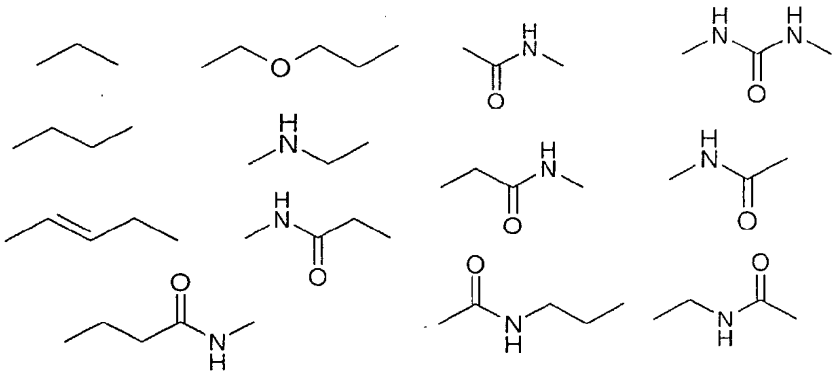
According to special embodiments of the invention, a, b and c are, independently from one another, an integer ranging from 0 to 2.

According to special embodiments, at least one -(NH)- moiety in the linker isolated from R^2 is replaced by at least one -(N)- moiety. In this special case, those skilled in the art will be able to adapt the number and type of bounds accordingly.

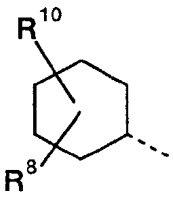
According to special embodiments of the invention, the linker isolated from R^2 is selected in the group consisting in :



According to particular embodiments of the invention, the "linker" in compounds of formula I is selected in the group consisting of :



According to special embodiments of the invention, R^1 is



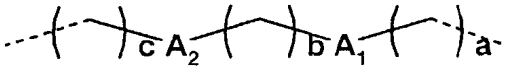
with R^{10} being H and R^8 being -Cl or -F.

According to special embodiments of the invention, R^9 is H.

According to special embodiments of the invention, R^9 and R^{9*} are, independently from one another, selected in the group of ethyl and methyl moieties.

According to special embodiments of the invention, R^8 and/or R^{10} is/are not an aromatic C_6 cycloalkyl.

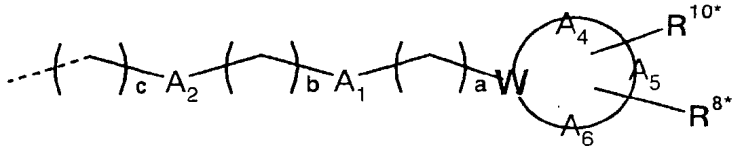
According to special embodiments of the invention, in :



- A_1 is -NH- ;
- A_1 is -NH- and c is 0 ; or
- A_1 is -NH- and A_2 is -CO- ; or
- A_1 is -NH-, A_2 is -CO- and c is 0.

According to special embodiments of the invention, the C_6 cycloalkyl moiety (e.g. a cyclohexyl or a phenyl moiety) or the C_7 cycloalkyl moiety (e.g. a cycloheptyl or a benzyl moiety), alone or in combination (e.g. $-(CH_2)_n-C_6$ cycloalkyl moiety, $-(CH_2)_n-C_7$ cycloalkyl moiety, $-O-(CH_2)_n-$ C_6 cycloalkyl moiety or a $-O-(CH_2)_n-C_7$ cycloalkyl moiety) is substituted, preferably at least with one moiety selected in the group consisting of R^8 and R^{10}.

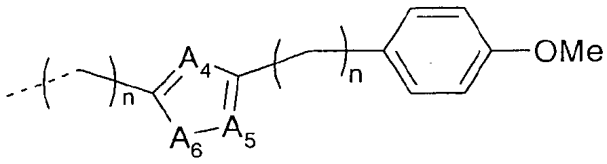
The above recitation describes a number of preferred moieties for the compounds of the present invention. Additionally, certain combinations of the above moieties will also be preferred. For example, in one group of embodiments, the compounds according to the present invention include those having R^2 being :

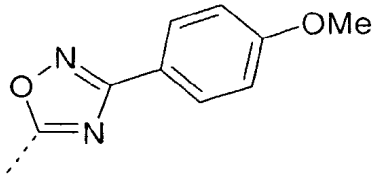


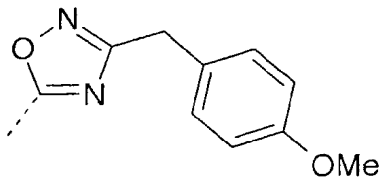
and having the following combinations of a, b, c, A_1 and A_2 in said R^2 :

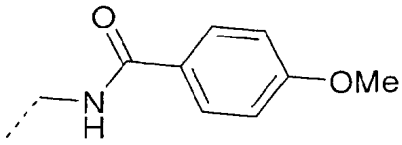
c	A_2	b	A_1	a
0	$-CH_2-$	1	$-CH_2-$ or $-CO-$	0
0	$-CH_2-$	1	$-CO-$	0
0	$-CH_2-$	1	$-CH_2-$	0
0	$-NR^9-$	0	$-CH_2-$ or $-CO-$	1
0	$-CH_2-$ or $-CO-$	0	$-NR^9-$	1
0	$-CO-$	0	$-NH-$	1
0	$-NR^9-$	0	$-CH_2-$ or $-CO-$	0
0	$-CH_2-$ or $-CO-$	0	$-NR^9-$	0
0	$-CO-$	0	$-CH_2-$	0
0	$-CH_2-$	0	$-CO-$	0
1	$-CH_2-$ or $-NR^9-$	0	$-CH_2-$ or $-CO-$	0
0	$-CH_2-$ or $-CO-$	0	$-CH_2-$ or $-NR^9-$	1
0	$-NR^9-$	0	$-CH_2-$ or $-CO-$	2
0	$-CH_2-$	0	$-CH_2-$	0
0	$-CH-$	1 with $(-CH-)_b$	$-CO-$	0
1 with $(-CH-)_c$	$-CH-$	0	$-CO-$	0

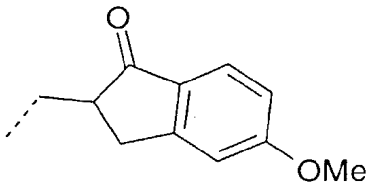
Examples of R^2 are selected in the group consisting of :

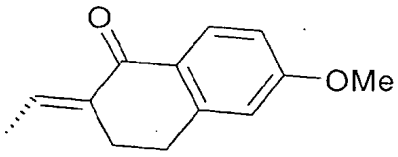


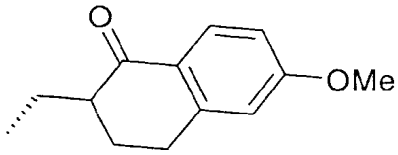


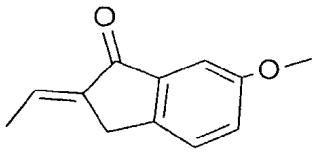


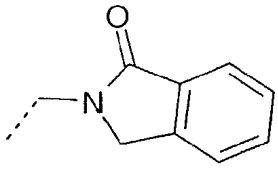


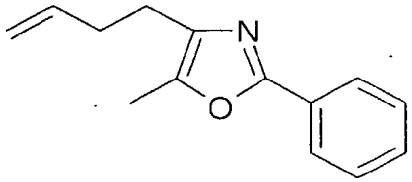


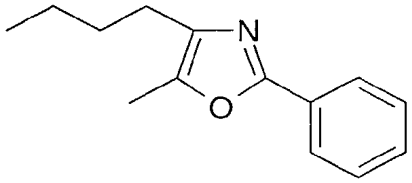












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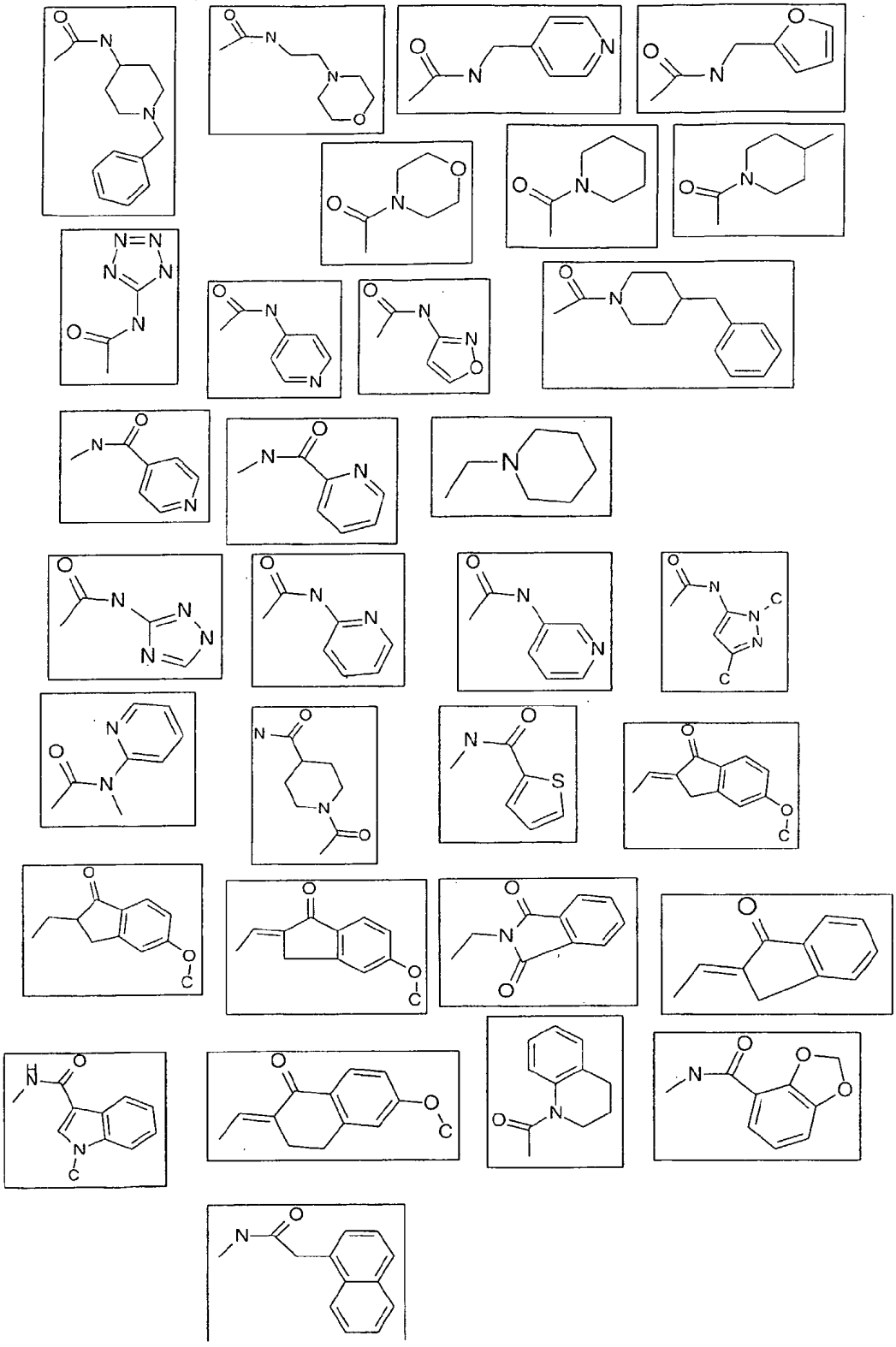
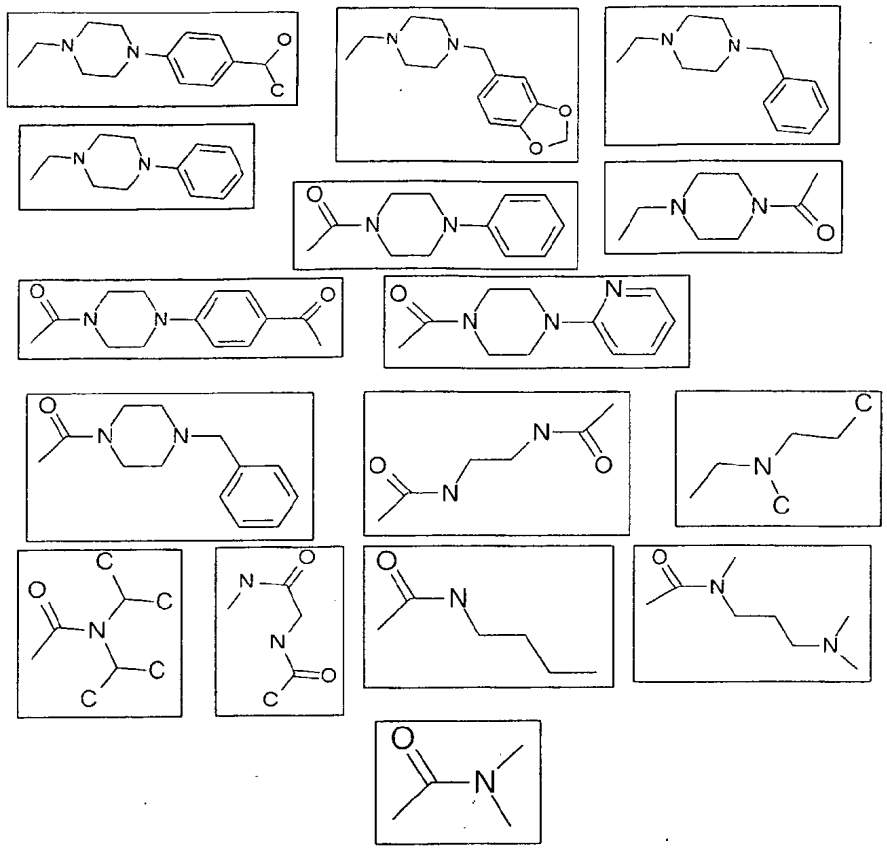
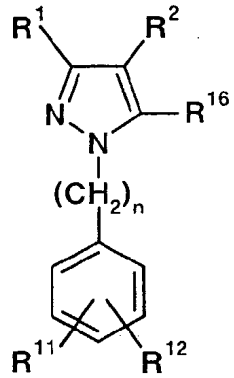


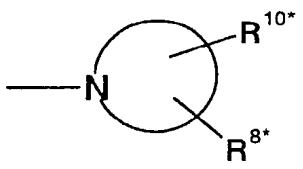


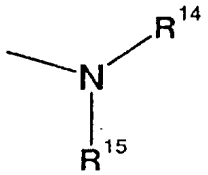
According to another embodiment, the present invention concerns compounds as above described which are further substituted with at least one moiety R^{16} in position 5 of the central pyrazole ring of Formula I :



said moiety R^{16} being selected in the group consisting of -Cl, -F, $-CF_3$, $-OCF_3$, $-COCF_3$, a C_{1-4} alkyl moiety (particularly ethyl or methyl).

As presented above, the R^2 moiety can include at least one amine which is either secondary or preferably tertiary :





According to specific embodiments, these amines are selected in the group consisting of : Dimethyl-amine; Diethyl-amine;Diisopropyl-amine; Dibenzyl-amine; Benzyl-methyl-amine ; Methyl-(4-nitro-phenyl)-amine; Methyl-(4-methoxy-phenyl)-amine; Methyl-(4-chloro-phenyl)-amine; Methyl-phenyl-amine; N,N,N'-Trimethyl-ethane-1,2-diamine; Methyl-p-tolyl-amine; Ethyl-phenyl-amine,Methyl-phenethyl-amine; N,N,N'-Trimethyl-propane-1,3-diamine; N,N-Dimethyl-2-methylamino-acetamide; Methyl-propyl-amine; 1,2,3,4-Tetrahydro-quinoline; 1,2,3,4-Tetrahydro-isoquinoline; Benzyl-phenyl-amine; Methyl-(2-nitro-phenyl)-amine; Ethyl-m-tolyl-amine; Methyl-o-tolyl-amine ;(3-Chloro-phenyl)-methyl-amine ;(3,4 -Dichloro-phenyl)-methyl-amine ; Piperidine ; morpholine ; 4-Methyl-piperidine ; 4-Benzyl-piperidine ; [1,4']Bipiperidinyl ; 1-Phenyl-piperazine ; 1-(4-Piperazin-1-yl-phenyl)-ethanone ; 1-(4-Methoxy-phenyl)-piperazine ; 1-(3-Methoxy-phenyl)-piperazine ; 1-Piperazin-1-yl-ethanone ; 1-Benzyl-piperazine.

According to particular embodiments, the compound of the invention is selected in the group consisting in :

2-(1-Methyl-1H-indol-3-yl)-N-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-acetamide (CRX000339);

Benzo[1,3]dioxole-4-carboxylic acid (1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-amide (CRX000329);

2-Naphthalen-1-yl-N-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-acetamide (CRX000330);

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid isoxazol-3-ylamide (CRX000238);

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (2,5-dimethyl-2H-pyrazol-3-yl)-amide (CRX000376);

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (3-methyl-isothiazol-5-yl)-amide (CRX000241);

1-Phenyl-4-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethyl)-piperazine (CRX000404) ;

6-Methoxy-2-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethylene)-indan-1-one (CRX000548);

N-(1-Phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethyl)-nicotinamide (CRX000538) ;

2-(1-Phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethyl)-isoindole-1,3-dione (CRX000466) ;

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (2-ethyl-2H-pyrazol-3-yl)-amide (CRX000148);

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (4-methoxy-6-methyl-pyrimidin-2-yl)-amide (CRX000260);

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (4-oxo-4,5-dihydro-thiazol-2-yl)-amide (CRX000244);

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (1H-[1,2,4]triazol-3-yl)-amide (CRX000354);

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (thiophen-2-ylmethyl)-amide (CRX000243);

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (5-methyl-furan-2-ylmethyl)-amide (CRX000265);

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (furan-2-ylmethyl)-amide (CRX000221);

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (3,4-dimethyl-isoxazol-5-yl)-amide (CRX000266);

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (1H-tetrazol-5-yl)-amide (CRX000177);

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (pyridin-4-ylmethyl)-amide (CRX000194);

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (pyridin-3-ylmethyl)-amide (CRX000267);

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (pyridin-2-ylmethyl)-amide (CRX000242);

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid pyridin-2-ylamide (CRX000355);

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid pyridin-3-ylamide (CRX000356);

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid pyridin-4-ylamide (CRX000187).

5-Methoxy-2-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethylene)-indan-1-one (CRX000405) ;

5-Methoxy-2-(1-phenyl-3-pyridin-3-yl-1H-pyrazol-4-ylmethylene)-indan-1-one (CRX000445)

6-Methoxy-2-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethyl)-benzo[d]isoxazol-3-one ;

5-Methoxy-3-methyl-2-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethyl)-inden-1-one;

5-Methoxy-2-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethyl)-inden-1-one ;

5-Methoxy-2-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethyl)-indan-1-one (CRX000440);

6-Methoxy-2-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethylene)-3,4-dihydro-2H-naphthalen-1-one (CRX000366) ;

2-(1-Phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethyl)-isoindole-1,3-dione (CRX000466) ;

2-(1-Phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethyl)-2,3-dihydro-isoindol-1-one ;

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (1-benzyl-piperidin-4-yl)-amide (CRX000153) ;

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (2-morpholin-4-yl-ethyl)-amide (CRX000154) ;

1-[4-(1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carbonyl)-piperazin-1-yl]-ethanone (CRX000161) ;

(3,4-Dihydro-2H-quinolin-1-yl)-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-methanone (CRX000162) ;

(1-Phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-piperidin-1-yl-methanone (CRX000164) ;

Morpholin-4-yl-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-methanone (CRX000166) ;

4-Methyl-piperidin-1-yl)-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-methanone (CRX000170) ;

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (1H-indazol-5-yl)-amide (CRX000175) ;

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (naphthalen-1-ylmethyl)-amide (CRX000193) ;

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)-amide (CRX000202) ;

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid naphthalen-2-ylamide (CRX000204) ;

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid indan-5-ylamide (CRX000219) ;

(4-Phenyl-piperazin-1-yl)-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-methanone (CRX000222) ;

1-{4-[4-(1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carbonyl)-piperazin-1-yl]-phenyl}-ethanone (CRX000223) ;

(1-Phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-(4-pyridin-2-yl-piperazin-1-yl)-methanone (CRX000224) ;

(3,4-Dihydro-1H-isoquinolin-2-yl)-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-methanone (CRX000225) ;

(4-Benzyl-piperazin-1-yl)-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-methanone (CRX000226) ;

[4-(4-Methoxy-phenyl)-piperazin-1-yl]-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-methanone (CRX000227) ;

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (1H-indol-5-yl)-amide (CRX000258) ;

4-(4-Methoxy-phenyl)-piperazin-1-yl]-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-methanone (CRX000269) ;

4-(1-Phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethyl)-morpholine (CRX000299) ;

4-Methyl-1-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethyl)-piperidine (CRX000300) ;

(4-Benzyl-piperidin-1-yl)-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-methanone (CRX000307) ;

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (2-methyl-1,3-dioxo-2,3-dihydro-1H-isoindol-5-1)-amide (CRX000309) ;

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid furan-2-ylmethyl-methyl-amide (CRX000311) ;

N-(1-Phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-nicotinamide (CRX000328) ;

N-(1-Phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-isonicotinamide (CRX000333) ;

Pyridine-2-carboxylic acid (1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-amide (CRX000334) ;

1-[4-(1-Phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethyl)-piperazin-1-yl]-ethanone (CRX000341) ;

1-(1-Phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethyl)-piperidine (CRX000343) ;

1-Benzyl-4-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethyl)-piperazine (CRX000352) ;

1-Methyl-1H-indole-3-carboxylic acid (1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-amide (CRX000377) ;

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid methyl-pyridin-2-yl-amide (CRX000381) ;

Thiophene-2-carboxylic acid (1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-amide (CRX000393) ;

1-Acetyl-piperidine-4-carboxylic acid (1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-amide (CRX000400) ;

1-Benzo[1,3]dioxol-5-ylmethyl-4-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethyl)-piperazine (CRX000403) ;

1-(4-Isopropyl-phenyl)-4-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethyl)-piperazine (CRX000438) ;

6-Methoxy-2-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethyl)-3,4-dihydro-2H-naphthalen-1-one (CRX000439) ;

2-(1-Phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethylene)-indan-1-one (CRX000470) ;

3-(4-Methoxy-phenyl)-5-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-[1,2,4]oxadiazole (CRX000459);

3-(4-Methoxy-benzyl)-5-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-[1,2,4]oxadiazole (CRX000513) ;

1-Phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethyl-ammonium (CRX000514) ;

N-(1-Phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethyl)-isonicotinamide (CRX000584) ;

Pyridine-2-carboxylic acid (1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethyl)-amide (CRX000575) ;

2-(1-Phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethyl)-2,3-dihydro-isoindol-1-one (CRX000602).

According to further particular embodiments, the compound of the invention is selected in the group consisting in :

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid butylamide (CRX000191) ;

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (2-acetylamino-ethyl)-amide (CRX000217) ;

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid ethylamide (CRX000239) ;

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (2-oxo-propyl)-amide (CRX000240) ;

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid [4-(2-oxo-propylamino)-butyl]-amide (CRX000257) ;

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (2-methoxy-ethyl)-amide (CRX000262) ;

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid diethylamide (CRX000268) ;

Diethyl-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethyl)-amine (CRX000279) ;

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (3-dimethylamino-propyl)-methyl-amide (CRX000298) ;

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid dibenzylamide (CRX000306) ;

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid dimethylamide (CRX000310) ;

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid methyl-propyl-amide (CRX000312) ;

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (3-dimethylamino-propyl)-methyl-amide (CRX000340) ;

Methyl-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethyl)-propyl-amine (CRX000353) ;

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid diisopropylamide (CRX000397) ;

2-Acetylamino-N-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-acetamide (CRX000399) ;

5-Methyl-2-phenyl-4-[3-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-allyl]-oxazole (CRX000783).

The terms "analogues, derivatives, solvates or salts of compounds of the present invention" includes both the structural derivatives and analogues of said compounds, their pharmaceutically acceptable solvates or salts, their stereoisomers, ester, prodrug form, or, their polymorphs. All these type of compounds are herein designated by the generic term "compounds".

Compounds of the Invention may be prepared by the application or adaptation of known methods, by which is meant methods used heretofore or described in the literature. General methods for preparing compounds according to the invention may also be prepared as described in the schemes

that are presented in the Experimental Section using readily available starting materials or known intermediates.

Those skilled in the art will recognize that the compounds of the present invention may be utilized in the form of a pharmaceutically acceptable salt thereof. The physiologically acceptable salts of the compounds of the Invention include conventional salts prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds of the present invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, formic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, perchloric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, lactic, propionic, isobutyric, palmoic, maleic, glutamic, hydroxymaleic, malonic, benzoic, succinic, glycolic, suberic, fumaric, mandelic, phthalic, salicylic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, hydroxynaphthoic, hydroiodic, and the like. Other acids such as oxalic, while not considered as pharmaceutically acceptable, may be useful in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable salts. When compounds of the present invention contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically

acceptable base addition salts include sodium, potassium, lithium, calcium, aluminium, ammonium, barium, zinc, organic amino, or magnesium salt, N,N^1-dibenzylethylenediamine, choline, diethanolamine, ethylenediamine, N-methylglucamine, procaine salts (e.g. chloroprocaine) and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (see, for example, Berge et al, "Pharmaceutical Salts", Journal of Pharmaceutical Science, 66, 1-19). Finally, certain specific compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

Similarly, those skilled in the art will recognize that the compounds of the present invention may be utilized in the form of a pharmaceutically acceptable solvate thereof. These solvates may be prepared by conventional methods such as dissolving the compounds of the Invention in solvents such as methanol, ethanol and the like, preferably water.

References hereinafter to a compound according to the invention include both compounds of Formula presented above and their pharmaceutically acceptable salts and solvates.

Additionally, those skilled in the art will recognize that the compounds of the invention may contain one or more chiral centers (stereocenters) and/or double bonds and, therefore, exist as stereoisomers, such as double-bond isomers (i.e., geometric isomers), enantiomers, or diastereomers. Accordingly, the present invention includes all possible stereoisomers including optical and geometric isomers of the above Formulae, and enantiomers. It further includes not only racemic compounds, or racemic mixture thereof, but also the optically active isomers as well. When a compound of the Invention is desired as a single enantiomer, it may be

obtained either by resolution of the final product or by stereospecific synthesis from either isomerically pure starting material or any convenient intermediate. Additionally, in situations where tautomers of the compounds of the Invention are possible, the present invention is intended to include all tautomeric forms of the compounds. These terms and methods required for identifying and selecting the desired compounds are well known in the art. For example, diastereoisomers may be separated by physical separation methods such as fractional crystallization and chromatographic techniques, and enantiomers may be separated from each other by the selective crystallization of the diastereomeric salts with optically active acids or bases or by chiral chromatography. Pure stereoisomers may also be prepared synthetically from appropriate stereochemically pure starting materials, or by using stereoselective reactions.

In special embodiments, e.g in the case of the -COOH being present, the compounds of the present invention might be in a prodrug form. A prodrug is in most cases a pharmacologically inactive derivative of a parent drug molecule that requires spontaneous or enzymatic transformation within the body in order to release the active drug, and that has improved delivery properties over the parent drug molecule. Therefore, prodrugs of a compound of the Invention is a compound which has chemically or metabolically cleavable groups and which readily undergoes chemical changes under physiological conditions to provide a compound of formula above described *in vivo*. Prodrugs include acid derivatives well known to practitioners of the art, such as, for example, alkyl esters prepared by reaction of the parent acid compound with a suitable alcohol, or amides prepared by reaction of the parent acid compound with a suitable amine. Particularly preferred alkyl esters as prodrugs are formed from methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tert-butyl,

morpholinoethyl, and N,N-diethylglycolamido. Methyl ester prodrugs, for example, may be prepared by reaction of the acid form of a compound of general formula (I) in a medium such as methanol with an acid or base esterification catalyst (e.g., NaOH, H_2 SO_4). Ethyl ester prodrugs are prepared in similar fashion using ethanol in place of methanol. Details regarding prodrugs are available for example in US 5,498,729.

Those skilled in the art are further able to prepare various polymorphs of a compound of the Invention for example by crystallization of compound of formula described above under different conditions. For example, he can use different solvents or mixtures commonly used for crystallization. Similarly, he can crystallize compounds of the Invention at different temperatures, according to various modes of cooling, ranging from very fast to very slow cooling during crystallizations. Polymorphs may also be obtained by heating or melting the compound followed by gradual or fast cooling. The presence of polymorphs may be determined by solid probe NMR spectroscopy, IR spectroscopy, differential scanning calorimetry, powder X-ray diffraction or such other techniques.

According to special embodiments, the compounds of the invention may be labeled in a variety of ways. For example, the compounds may contain radioactive labels e.g. radioactive isotopes such as, for example H^3 (tritium) or C^{14} at one or more of the atoms that constitute compounds of the general formula presented above. Such radioactively labelled compounds constitute very specific embodiments of the invention and may be administered systematically, or locally, to an animal, preferably a human. These labelled compounds are useful, for example, for imaging the *in vivo* levels and/or localization of PPAR-beta in tissues and tissue sections e.g. by the use of well known techniques e.g. autoradiographic techniques or scintigraphy. Principles of radioligand binding and receptor

autoradiography are well known in the art. As an alternative the compound may be labelled with any other type of label that allows detection of the substance, e.g. a fluorescent label or biotin, and the resulting compound can be used for the similar purpose as the radioactively labelled compound. Similarly, the compounds may be advantageously joined, covalently or noncovalently, directly or through a linker molecule, to a wide variety of other moieties, which may provide function as carriers, labels, adjuvents, coactivators, stabilizers, etc. Such labeled and joined compounds are contemplated within the present invention.

The invention further concern composition comprising at least one compound of the general formula as above disclosed.

The compounds and compositions of the present invention are further characterized by their properties towards nuclear receptor PPARs. More specifically, the Applicant has shown that the compounds of the Invention are first able to interact with at least one PPAR receptor, more preferably with PPAR-gamma ; they are thus named PPAR or PPAR-gamma ligand, respectively. More preferred compounds are those, which are able to interact at least with the ligand binding domain (LBD) of a PPAR receptor, more preferably with the LBD of PPAR-gamma (i.e. amino acids 195-475). In even more preferred embodiments, the compounds of the invention are those which bind to the LBD of a PPAR receptor, more preferably PPAR-gamma, with an affinity of at least about 2 uM and more than about 1 nM, with concentrations in the range of about 10 up to 500 nM being preferred.

Methods and conditions for testing or measuring the interacting and/or binding property of compounds (e.g. ligands) with nuclear receptors and/or LBD are widely disclosed and implemented in the art : for examples, Glickman et al., 2002, J. Biomolecular Screening, 7, 3-10 or Lehmann et

al., 1995, J. Biol. Chem., 270, 12953-12956. For example, Le Douarin et al., (2001, Methods Mol. Biol., 176, 227-48) have disclosed an *in vitro* screening test using the yeast two-hybrid system that is based on the ligand-dependent interaction of two proteins, a hormone receptor and a coactivator ; Zhou et al., (2001, Methods, 25, 54-61) have disclosed a homogeneous time-resolved fluorescence (HTRF) energy transfer technology which is sensitive, homogeneous, and nonradioactive ; Beaudet et al., (2001,Genome Res., 11, 600-8) have disclosed the AlphaScreen™ technology (Packard BioScience) which allows the development of high-throughput homogeneous proximity assays. The full content of these papers is incorporated herein by reference. Specific examples of said standard procedures available in the art are the Fluorescence Resonance Energy Transfer (FRET), the CoActivator-dependent Receptor Ligand Assay (CARLA) and the GST-pull down assays or two-hybrid assays (see Experimental Section).

According to another embodiment, the compounds of the present invention are able to interact with said nuclear receptors and/or related LBD in a ligand-dependent fashion so as to effect transcriptional activation or so as to inhibit or silence transcription of genes which are transcriptionally modulated by the said nuclear receptors; i.e. the compounds and compositions of the present invention are able to modulate the transcriptional activity of PPAR receptors, more preferably PPAR-gamma, and thus the biological effects mediated by these nuclear receptors.

Ability of compounds and compositions of the invention to specifically modulate the transcriptional activity of PPAR receptors, more preferably PPAR-gamma, may be first evaluated *in vitro* for their ability to modulate PPAR receptor biological effects using biochemical assays (see, for example, the assays above mentioned; e.g. AlphaScreen™ technology) or in cell-based assays. For example, a system for reconstituting

ligand-dependent transcriptional control has been developed by Evans et al., 1988, Science, 240, 889-95 and has been termed "co-transfection" or "cis-trans" assay. This assay is described in more detail in U.S. 4,981,784 and US 5,071,773, which are incorporated herein by reference. Also see Heyman et al., 1992, Cell, 68, 397-406, Kliewer et al., 1995, Cell 83, 813-819 , Lehmann et al., 1995, J. Biol. Chem., 270, 12953-12956, or Lehnman et al. 1997, J. Biol. Chem., 272, 3137-3140. The co-transfection assay provides a method to evaluate the ability of a compound to modulate the transcriptional response initiated by a nuclear receptor, for example PPAR. The co-transfection assay is a functional, rapid assay that monitors hormone or ligand activity, is a good predictor of the *in vivo* activity, and can be used to quantitate the pharmacological potency and utility of such ligands in treating various disease states (Berger et al., 1992, J. Steroid Biochem Molec. Biol., 41, 733-38). Briefly, the co-transfection assay involves the introduction of various plasmids by transient transfection into a mammalian cell : at least a plasmid which contains a nuclear receptor receptor cDNA (e.g. PPAR gamma) and directs constitutive expression of the encoded receptor ; and at least a plasmid which contains a cDNA that encodes for a readily quantifiable protein, e.g., firefly luciferase or chloramphenicol acetyl transferase (CAT), alkaline phosphatase (SPAP or SEAP), under control of a promoter containing a PPAR response element (PPRE), which confers dependence on the transcription of the reporter. This assay can be used to accurately measure efficacy and potency of interaction and modulating activity of a specific ligand compound. Alternatively, the compounds and compositions can be evaluated for their ability to increase or decrease gene expression modulated by PPAR, using western-blot analysis.

Alternatively, Voegel et al. (1998, EMBO J. 17, 507-519) have proposed the use of transient transfection assays with a

GAL4 reporter plasmid and chimeras containing various peptide fragments linked to the GAL4 DBD (DNA Binding Domain).

According to special embodiments, the compounds of the present invention achieve no activation of other PPAR isoform (e.g. PPAR alpha, PPAR beta) and other known target i.e. PXR, RXR , especially at a dose of 10 µM.

It is further possible to analyze the modulating properties of the compounds and compositions of the present invention *in vivo*, in established animal models. These models are particularly useful to evaluate the effects of said compounds and compositions on plasma levels of glucose, insulin, total cholesterol, triglycerides and non-esterified free fatty acids (NEFA's), on weight variation, on oedema or hepatotoxicity occurrence, etc... These models are well known in the art (e.g. db/db mice, Zucker fa/fa rat, KKY or KKAY mice, NOD or non-obese diabetic mice, DIO models...).

According to a specific embodiment, the compounds and compositions of the present invention are PPAR and/or PPAR LBD agonists. According to a preferred embodiment, the compounds and compositions of the present invention are PPAR-gamma and/or PPAR-gamma LBD agonists. By "agonist " is meant a compound or composition which when combined with an intracellular receptor stimulates or increases a reaction typical for the receptor, e.g., transcription activation activity. In one embodiment, said agonist is a PPAR-gamma agonist, i.e. a PPAR ligand which potentiates, stimulates, induces or otherwise enhances the transcriptional activity of a PPAR-gamma receptor, e.g., such as by mimicking a natural physiological ligand for the receptor.

According to another preferred embodiment, the compounds and compositions of the present invention are PPAR and/or PPAR LBD partial-agonists, and more particularly, the compounds and compositions of the present invention are PPAR-gamma and/or

PPAR-gamma LBD partial-agonists. A drug that produces less than the possible maximal effect (i.e. the maximal effect produced by a full agonist, or reference molecule) is called partial agonist.

For example, the partial agonist property of the compounds and compositions of the present invention can be defined by reference to rosiglitazone (Avandia™, GlaxoSmithKline) which is a full agonist. According to special embodiments, the compounds and compositions of the present invention are partial agonists in the sense that their maximal efficacy (illustrated by their Vmax and/or Emax) is less than about 70% of the maximal efficacy (illustrated by Vmax and/or Emax) of the rosiglitazone measured under identical conditions (see the Experimental section). In preferred embodiments, their maximal efficacy is comprised between about 50% and about 10% of the rosiglitasone maximal efficacy, and in rather preferred embodiments it is comprised between about 30% and about 20% of the rosiglitasone maximal efficacy.

Potency and efficacy are the two key features in analyzing ligand agonist, including partial agonist, property. Potency can be calculated through dose response experiment in a given functional assay e.g. co-transfection assay. It represents the dose of compound necessary to achieve 50 % of maximal affect (EC50). This value is closely related to the Kd obtained in a binding assay and therefore related to the affinity of the compound for the receptor. Identification of compounds with low potency is important to achieve target specificity and the development of low dosed pharmaceutical compositions to be administered into patients. Efficacy determines the maximum effect that can be achieved in a functional assay that assesses the compound tested effect on the PPAR, and more particularly PPAR-gamma, in a co-transfection assay. The Applicants postulate that too high level of efficacy can be associated with detrimental

undesirable side effects. Thus, they proposed to seek for potent PPAR ligands, especially PPAR-gamma ligands, with reduced efficacy (compared to rosiglitazone for example) which should result in safer drugs.

According to special embodiments, the compounds and compositions of the present invention have a potency comprised between about 1 nM and 2 uM, with concentrations in the range of about 10 up to 500 nM being preferred.

According to other embodiments, the compounds and compositions of the present invention are both PPAR and/or PPAR LBD partial-agonists and PPAR and/or PPAR LBD antagonists. More particularly, the compounds and compositions of the present invention are both PPAR-gamma and/or PPAR-gamma LBD partial-agonists and PPAR-gamma and/or PPAR-gamma LBD antagonists. By "antagonist" is meant a compound or composition which when combined with an nuclear receptor interferes or decreases a reaction typical for the receptor, e.g., transcription activation activity. The term "PPAR-gamma antagonist" designates a PPAR-gamma ligand that gives greater than 50% inhibition of transactivation achieved by 100 nM rosiglitazone when tested in the cell-based reporter assay such as described in WO 01/17994. As general definition, "PPAR antagonist" designates a PPAR ligand which can inhibit the activity of a corresponding PPAR agonist. More generally, these agonist/antagonist/partial agonist activities may be measured by assays widely known to one skilled in the art such as for example those which are disclosed in WO99/50664 or WO96/41013.

The compounds and compositions of the invention are further characterized by their biological activities, and more specifically present beneficial activities towards glucose cellular uptake and/or adipogenesis. For example, it has been shown that compounds that activate PPAR-gamma (e.g.

thiazolidinediones) are further inducing adipocyte differentiation (i.e. adipogenic effect) and are thus resulting in body weight increase in treated patients. Therefore it is highly desirable that the next generation of such compounds are devoid of such activity. These activities can be appreciated using methods widely used in the art (see for example tests in the mouse 3T3L1 in Mukherjee et al., 2000, Mol. Endo., 14, 1425-1433). More specifically, these activities are appreciated with reference to a molecule which has already been identified in the art, such as rosiglitazone. According to a preferred embodiment of the invention, the claimed compounds and compositions display at least about 50%, preferably at least about 60%, more preferably at least about 70 % and even more preferably at least about 80% of the rosiglitazone property towards glucose uptake. Ideally, it will be 100% or more. According to another preferred embodiment of the instant invention, the claimed compounds and compositions display less than about 50%, preferably less than about 40%, more preferably less than about 30 % and even more preferably less than about 20% of the rosiglitazone property towards adipogenesis.

It is now widely acknowledged that nuclear receptors, such as PPAR-gamma, achieve trancriptional activation or repression by binding to cognate sequences in the promoter regions of target genes (e.g. PPREs) and by recruiting numerous cofactor complexes whose activities range from chromatin remodeling, histone and cofactor modification, to basic transcription machinery recruitment (Glass, & Rosenfeld, 2000, Genes Dev., 14, 121-141). These cofactors may to a large extend determine the specificity of the action of nuclear receptors and integrate their action in a network of stimuli whose proper orchestration leads to a specific cellular response. Hence, the determination of the multiple partnerships in which each nuclear receptor is engaged, as a

function of time and cell type, is a crucial aspect leading to a better understanding of the activity of nuclear receptors on transcriptional regulation. For instance, it is known that for certain hormones, such as estrogen, the response to the hormone is determined almost to the same extent by the presence of the respective nuclear hormone receptor, as by the presence of the cofactors, which interact with the receptors.

Various PPAR cofactors have been identified so far. Some cofactors such as p300/CBP (Dowell et al., 1997, J. Biol. Chem. 272, 33435-33433), SRC-1 (Onate et al., 1995, Science 270, 1354-1357), TIF2 (GRIP-2 ; Chakravarti et al., 1996, Nature, 383, 99-103), SRA (Lanz et al., 1999, Cell, 97, 17-27), AIB-1 (Anzick et al., 1997, Science, 277, 965-968), TRAP220/DRIP205 (i.e. PBP ; Zhu et al., 1997, J. Biol. Chem. 272, 25500-25506 ; Rachez et al., 1999, Nature, 398, 824-828), PGC-1 (Puigserver et al., 1998, Cell 92, 829-839), PRIP (Zhu et al., 2000, J. Biol. Chem. 275, 13510-13516), PGC-2 (Castillo et al., 1999, Embo J. , 18, 3676-3687), ARA70 (Heinlein et al., 1999, J. Biol. Chem. 274, 16147-16152), RIP140 (Treuter et al., 1998, Mol. Endocrinol. 12, 864-881), enhance their transcriptional activity, whereas SMRT (Lavinsky et al., 1998, Proc. Natl. Acad. Sci. USA 95, 2920-2925) and N-CoR (Dowell et al., J. Biol. Chem 274, 15901-15907) repress it. Additionally, it has been shown that members of the PPAR-gamma cofactor family (e.g. the 160-kDa protein (SRC-1/TIF2/AIB-1), CBP/p300 or TRAP220/DRIP205) interact directly with PPAR-gamma and potentiate nuclear receptor transactivation function in a ligand-dependent fashion leading to biological action or side effects that can differ according to the ligand used (Adams et al., 1997, J. Clin. Invest., 100, 3149-3153). Kodera et al. (2000, J. Biol. Chem., 275, 33201- 33204) have examined whether interactions between PPAR-gamma and known cofactors were induced to the same extent by different classes of PPAR-gamma ligands (natural and

synthetic) and concluded that the overall structure of PPAR-gamma and cofactors complexes may be different according to the ligands involved, resulting in the activation of a particular set of target gene promoters that exert different biological actions.

The p160 family of cofactors, composed of SRC-1, TIF2 and SRC-3, is of notable interest for PPAR-gamma. SRC-1 was initially isolated as a progesterone receptor (PR) coactivator (Onate et al., 1995, Science, 270, 1354-1357) but has been shown later to also interact in a yeast two-hybrid system with the PPAR-gamma Ligand Binding Domain (Zhu et al, 1996, Gene Expression, 6, 185-195). Like CBP/p300, SRC-1 has an intrinsic histone acetyltransferase activity (Spencer et al.,1997, Nature, 389, 194-198) and is broadly expressed albeit at different levels (Misiti et al., 1998, Endocrinology , 139, 2493-2500). SRC-1 has been shown to have two PPAR binding domains, each containing the LXXLL consensus receptor interaction motif (Heery et al., 1997, Nature, 387, 733-736). The related members of the p160 family of cofactors, TIF2 (Voegel et al., 1998, EMBO J. 17, 507-519) and SRC-3 (Torchia, et al., 1997, Nature, 387, 677-684), have been shown to also interact with PPAR-gamma in a manner similar to SRC-1.

The Applicant has now investigated whether these different p160 family members can be specifically recruited by the compounds and compositions of the invention. Thus, according to special embodiments, the compounds and compositions of the present invention are furthermore characterized by a restricted cofactor(s) recruitment pattern. In preferred embodiments, said pattern results actually in distinct effects on the regulation of the transcriptional activity of said nuclear receptors allowing a very fine tuned regulation which results in the activation of specific metabolic processes as well as the elimination of unwanted side effects. In more specific embodiments, the compounds and

compositions of the present invention are furthermore able to inhibit the interaction of PPAR receptor, more preferably PPAR receptor LBD, with cofactor TIF2 and that enhance the interaction of PPAR receptor, more preferably PPAR receptor LBD, with cofactor SRC-1. Preferably, said PPAR receptor is PPAR-gamma receptor. Methods for measuring inhibition and/or enhancement of cofactor recruitment by ligands are detailed in co-pending application EP 02291496.4 filed on June 14, 2002. The Alphascreen™ method is a proximity assay that allow the measurement of the interaction of a nuclear receptor associated with a at least one ligand and with at least one cofactor. In a preferred embodiment, the agonist / partial agonist / antagonist compounds of the invention when bound to PPAR-gamma will allow to recruit SRC1 to the LBD with an EC50 which is at least one log greater than the one for TIF2, with 2 log being preferred. This type of analysis is widespread practice of the one skilled in the art.

The compounds and compositions of the present invention due to their agonistic, particularly partial agonistic, or antagonistic property towards natural physiological ligands of the PPAR receptors, especially PPAR-gamma receptor, can serve as pharmaceuticals for controlling the biological effects of PPAR-mediated transcriptional control and the attendant physiological effects produced thereby. More specifically they are capable of specifically modulating a cellular physiology to reduce an associated pathology or provide or enhance a prophylaxis.

Accordingly, the present invention further concerns a composition comprising at least one compound of the invention as disclosed above and a pharmaceutically acceptable carrier or diluent. These pharmaceutical compositions may be prepared by conventional techniques, e.g. as described in Remington, 1995, The Science and Practise of Pharmacy, 19.sup.th Ed.

Typical compositions of the present invention are associated with a pharmaceutically acceptable excipient which may be a carrier or a diluent or be diluted by a carrier, or enclosed within a carrier which can be in the form of a capsule, sachet, paper, tablets, aerosols, solutions, suspensions or other container. In making the combination products, conventional techniques for the preparation of pharmaceutical compositions may be used. For example, the active compounds will usually be mixed with a carrier or a diluent, or diluted by a carrier or a diluent, or enclosed within a carrier or a diluent which may be in the form of a ampoule, capsule, sachet, paper, tablets, aerosols, solutions, suspensions or other container. When the carrier serves as a diluent, it may be solid, semi-solid, or liquid material which acts as a vehicle, excipient, or medium for the active compound. The active compounds can be adsorbed on a granular solid container for example in a sachet. Typically, liquid oral pharmaceutical compositions are in the form of, for example, suspensions, elixirs and solutions; solid oral pharmaceutical compositions are in the form of, for example, powders, capsules, caplets, gelcaps and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed.

Some examples of suitable carriers or diluents are, without being limited, water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, peanut oil, olive oil, gelatine, lactose, terra alba, sucrose, cyclodextrin, amylose, magnesium stearate, talc, gelatin, agar, pectin, acacia, stearic acid or lower alkyl ethers of cellulose, silicic acid, fatty acids, fatty acid amines, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, polyoxyethylene, hydroxymethylcellulose and polyvinylpyrrolidone.

Similarly, the carrier or diluent may include any sustained release material known in the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax. The formulations may also include wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents or flavoring agents. The formulations of the invention may be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art. In one embodiment, the active compounds are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc. The compound of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of lipids, including but not limited to amphipathic lipids such as phosphatidylcholines, sphingomyelins, phosphatidylethanolamines, phophatidylcholines, cardiolipins, phosphatidylserines, phosphatidylglycerols, phosphatidic acids, phosphatidylinositols, diacyl trimethylammonium propanes, diacyl dimethylammonium propanes, and stearylamine, neutral lipids such as triglycerides, and combinations thereof. They may either contain cholesterol or may be cholesterol-free. These can be prepared according to methods known to those skilled in the art, for example, as described in US 4,522,811. The pharmaceutical compositions of the

invention can be sterilized and mixed, if desired, with auxiliary agents, emulsifiers, salt for influencing osmotic pressure, buffers and/or coloring substances and the like, which do not deleteriously react with the active compounds.

The pharmaceutical compositions of the invention will typically be those which contain an effective amount of a compound of the invention. In general, an effective amount of a compound of the invention is a concentration of the said compound that will produce a 50% (EC_{50}) increase in PPAR activity in a cell-based reporter gene assay, or a biochemical peptide sensor assay such as the assays described above.

For example, the pharmaceutical compositions herein may contain between about 0.1 mg and about 1000 mg, preferably about 100 to about 500 mg, even more preferably about 5 to about 50 mg, of the compound, and may be constituted into any form suitable for the mode of administration selected. The tablets or pills of the pharmaceutical composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids with such materials as shellac, alcohol and cellulose acetate.

Alternatively, the composition of the present invention further comprises a natural or synthetic PPAR and/or RXR agonist or antagonist.

Naturally occurring ligands that modulate the activity of PPAR, preferably the PPAR-gamma, include but are not limited

to, fatty acids such as arachidonic acid derivatives or metabolites such as eicosanoids (e.g. various isomeric forms of 8-hydroxytetraenoic acid) and cyclopentenone prostaglandins (e.g. prostaglandins in the J and A series and their metabolites), long-chain fatty acids and their derivatives, e.g. 9- and 13-cis-hydroxyoctadecadienoic acid (HODE) (Nagy et al., 1998, Cell, 17, 93, 229-240 ; Chinetti et al., 2001, Z. Kardiol, 90, Suppl 3, 125-32). Diterpene acids and auronols (e.g. pseudolaric acids A and B) isolated from Pseudolarix kaempferi (Pan et al., 1990, Planta. Med., 56, 383-385; Li et al., 1999, J. Nat. Prod., 62, 767-769) have also been shown to activate PPAR-gamma and are expected to be useful in the practice of this invention. In one embodiment, said natural PPAR ligand is a prostaglandin J2 or delta-12-prostaglandin J2 (PGJ2) metabolite, and more particularly it is 15-deoxy-delta-12,14-prostaglandin J2 [15-deoxy-Delta(12,14)-PGJ(2) or 15d-PGJ2].

Synthetic ligands that modulate the activity of PPAR are for example antidyslipidemic fibrates (e.g. clofibrate, fenofibrate, benzofibrate, ciprofibrate, gemfibrozil), thiazolidine derivatives (e.g. thiazolidinediones), oxazolidine derivatives (e.g. oxazolidinediones), alpha-alkylthio, alpha-alkoxy and carboxylic acid derivatives of thiazolidines and oxazolidines (Hulin et al. 1996, J. Med. Chem., 39, 3897-3907), N-2-L-tyrosine derivatives (e.g. N-(2-Benzoylphenyl)-L-tyrosine ; Henke et al., 1998, J. Med. Chem., 41, 5020-5036), FMOC-L-Leucine (WO0200611), phenyl acetic acid derivatives (Berger et al., 1999, J. Biol. Chem., 274, 6718-6725) and indole-thiazolidinedione derivatives (Lohray et al., 1998, J. Med. Chem., 41, 1619-1630).

Compounds disclosed or described in the following articles, patents and patent applications which have RXR agonist activity are incorporated by reference herein: US 5,399,586 and 5,466,861, WO96/05165, WO94/15901, WO93/11755;

WO94/15902, WO93/21146, Boehm, et al. 1994, J. Med. Chem., 38, 3146-3155, Boehm, et al. 1994, J. Med. Chem., 37, 2930-2941, Antras et al., 1991, J. Biol. Chem., 1266, 1157-1161. RXR specific agonists include, but are not limited to, 9-cis-retinoic acid, 4-(1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-ethenyl)benzoic acid (3-methyl-TTNEB; LGD 1069), LG 100268 (i.e. 2-[1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-cyclopropyl]-pyridine-5-carboxylic acid), 4-[(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthy)-2-carbonyl]-benzoic acid, ((E)-2-(2-((5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthyl)propen-1- yl)-4-thiophenecarboxylic acid) (AGN 191701), 2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-2-(carboxyphenyl)-1 ,3-dioxolane (SR 11237), 4-(5H-2,3-(2,5-dimethyl-2,5-hemano)-5-methyl-dibenzo(b,e) (1,4)diazepin-11-yl)-benzoic acid (HX600) or thiadiazepin analogues thereof, 3,7,11,15-tetramethyl hexadecanoic acid (phytanic acid), 6-(1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)cyclopropyl) nicotinic acid, ALRT 1057 (i.e. 9-cis retinoic acid, 2-(4-carboxyphenyl)-2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalen yl)-1,3-dithiane (SR11203), 4-(2-methyl)-1-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)propenyl)benzoic acid (SR11217), and the like or a pharmaceutically acceptable salt thereof.

Likewise, the compositions of the present invention can further comprise additional agents. Examples of such additional agents are hypoglycemic agents (e.g. sulfonylurea or/and biguanide derivatives), insulin, insulin derivative, insulin secretagogue, insulin sensitizer, or insulin mimetic ; other examples are mitotic inhibitors, alkylating agents, antimetabolites, nucleic acid intercalating agents, topoisomerase inhibitors, agents which promote apoptosis, or agents which increase immune responses to tumors (e.g cytokine chosen from alpha-, beta- and gamma-interferon, interleukins,

and in particular IL-2, IL-4, IL-6, IL-10 or IL-12, tumour necrosis factors (TNFs) and colony stimulating factors (for example GM-CSF, C-CSF and M-CSF). Literature provides to the skilled man with numerous examples of such additional agents.

The compounds and compositions containing the same of the present invention exhibit agonist, and preferably partial-agonist activity toward PPAR receptors, and preferably towards PPAR-gamma receptor, which are important factors at the top of a gene cascade involved in differentiation of adipocytes, synthesis, accumulation, metabolism and decomposition of lipids, control of glucose metabolism, and thermogenesis in the body.

Accordingly, the compounds and compositions of the present invention are specially adapted to cure, improve or prevent one or more symptoms of diseases or pathologic conditions associated with cells types that express PPAR nuclear receptors. Thus, a further aspect of the present invention is a method for the treatment of a mammal, including man, in particular in the treatment of diseases and conditions where modification of the effects of PPAR, preferably PPAR-gamma, is of therapeutic benefit, the method comprising administering to the patient in need a therapeutically effective amount of at least one compound of Formula (I), derivate thereof, or a pharmaceutically composition as above disclosed. It will be appreciated by those skilled in the art that the term "treatment" herein extends to prophylaxis as well as the treatment of established diseases or symptoms.

"Diseases and conditions where modification of the effects of PPAR is of therapeutic benefit" means diseases or pathologic conditions wherein the observed disorder is associated initially with the deregulation, disturbance, hypersensitivity, or malfunctioning of cells expressing PPAR nuclear receptors, preferably PPAR-gamma receptor, or more

specifically in which the disease or pathologic conditions is caused by one or more genes that are under the transcription control of PPARs, preferably of PPAR-gamma, or said disease or pathological condition causing genes are post-translationally modified in response to PPARs. Examples of these cells are those from liver, skeletal muscle, kidney, heart, CNS, adipose tissues, intestine, or cells of the monocyte lineage. In preferred embodiment, said cell type is an adipocyte or pre-adipocyte. Another example is a PPAR-responsive hyperproliferative cell. Examples of these diseases or pathologic conditions are those associated with impaired metabolism of glucose, cholesterol or triglycerides. More specifically, it is insulin resistance, Type II diabetes, Type I diabetes, impaired glucose tolerance, dyslipidemia, hyperlipidemia, hypercholesterolemia, hypertriglycidemia, disorders related to the metabolic disease, Syndrome X including hypertension, obesity, hyperglycaemia, atherosclerosis, thrombosis, hyperlipidemia, coronary artery disease, heart failure and other cardiovascular disorders ; renal diseases including glomerulonephritis, glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis ; neurologic diseases or dementia ; anorexia bulimia, anorexia nervosa ; inflammatory diseases such as cutaneous disorders (including acne vulgaris, psoriasis, cutaneous disorders with barrier dysfunction, cutaneous effects of aging, poor wound healing), diabetic complications, polycystic ovarian syndrome (PCOS) and bone loss, e.g. osteoporosis ; gastrointestinal diseases ; viral, proliferative cells or tumoral diseases, such as cancers.

According to one embodiment of the present invention, there is provided a method for treating obesity, said method comprising administering to a patient in need of such treatment an amount of at least one compound or a composition of the invention effective to block cell differentiation to

produce lipid-accumulating cells. Obesity is a disease that had become highly prevalent in affluent societies and in the developing world and which is a major cause of morbidity and mortality. It is characterized by a body mass index above 25 but those of skill in the art readily recognize that the invention method is not limited to those who fall within the above criteria. Thus there is a strong need for efficient therapy to treat this disease which has been identified as a leading cause of coronary heart disease, Type II diabetes, stroke, hyperlipidemia, gout, osteoarthritis, reduced fertility and many other psychological and social problems. Additionally, obesity contributes to insulin resistance and diabetes.

Those of skill in the art recognize that there are numerous cell types which are capable of differentiation to produce "lipid-accumulating cells," such as, for example, mesenchymal cells (e.g., fibroblasts). The terms "amount of ... produce lipid-accumulating cells" refers to levels of compound of the invention sufficient to provide circulating concentrations high enough to accomplish the desired effect. Such a concentration typically falls in the range of about 10 nM up to 2 uM; with concentrations in the range of about 100 nM up to 500 nM being preferred. Since the activity of different compounds which fall within the definition of structure I as set forth above may vary considerably, and since individual subjects may present a wide variation in severity of symptoms, it is up to the practitioner to determine a subject's response to treatment and vary the dosages accordingly.

In another embodiment, disease or pathologic condition according to the invention is diabetes or insulin resistance. Insulin resistance is manifested by the diminished ability of insulin to exert its biological action across a broad range of concentrations. During early stages of insulin resistance, the body secretes abnormally high amounts of insulin to compensate

for this defect. Within developed countries, diabetes mellitus has become a common problem and is associated with a variety of abnormalities including, but not limited to, obesity, hypertension, hyperlipidemia and renal complications. It is now increasingly being recognized that insulin resistance and hyperinsulinemia contribute significantly to obesity, hypertension, atherosclerosis and Type II diabetes mellitus. The association of insulin resistance with obesity, hypertension and angina pectoris has been described as a syndrome (Syndrome-X) in which insulin resistance plays the central role. The term "diabetes" refers to all variant forms of diabetes mellitus (DM), including Type I DM, Type II DM, gestational diabetes, juvenile diabetes, etc.

Accordingly, in still another embodiment of the present invention, there is provided a method for modulating insulin-sensitivity and blood glucose levels in a patient, said method comprising administering to a patient in need of such treatment an amount of at least one compound or composition of the invention in effective to lower the blood glucose level of said subject. As employed herein, the phrase "amount . . . effective to lower blood glucose levels" refers to levels of compound of the present invention sufficient to provide circulating concentrations high enough to accomplish the desired effect. Such a concentration typically falls in the range of about 10 nM up to 2 uM; with concentrations in the range of about 100 nM up to 500 nM being preferred. As noted previously, since the activity of different compounds of the present invention which fall within the definition of structure I as set forth above may vary considerably, and since individual subjects may present a wide variation in severity of symptoms, it is up to the practitioner to determine a subject's response to treatment and vary the dosages accordingly.

In another embodiment, disease or pathologic condition according to the invention is hyperlipidemia. Hyperlipidemia is considered the primary cause of cardiovascular and other peripheral vascular diseases. An increased risk of cardiovascular disease is correlated with elevated plasma levels of LDL (Low Density Lipoprotein) and VLDL (Very Low Density Lipoprotein) as seen in hyperlipidemia. Numerous studies have shown that lowering of plasma triglycerides and total cholesterol, in particular LDL and VLDL and increasing HDL cholesterol leads to a significant reduction of cardiac events.

In yet another embodiment, the diseases or pathologic conditions according to the invention also include cellular proliferation, growth, differentiation, or migration disorders. As used herein, a "cellular proliferation, growth, differentiation, or cell migration disorders" is a disorder in which a cell increases in number, size or content, in which a cell develops a specialized set of characteristics which differ from that of other cells, or in which a cell moves closer to or further from a particular location or stimulus. The PPAR molecules of the present invention are involved in signal transduction mechanisms, which are known to be involved in cellular growth, differentiation, and migration processes. Thus, the PPAR molecules may modulate cellular growth, differentiation, or migration, and may play a role in disorders characterized by aberrantly regulated growth, differentiation, or migration. Such disorders include cancer, e.g., carcinomas, sarcomas, leukemias, and lymphomas; tumor angiogenesis and metastasis; skeletal dysplasia; hepatic disorders; and hematopoietic and/or myeloproliferative disorders. Exemplary disorders include, but not limited to, fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma,

mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, and retinoblastoma.

In other embodiments, the disease or pathologic condition according to the invention is a disorder characterized by aberrant cell growth of PPAR-responsive cells such as hyperplastic or neoplastic disorders arising in adipose tissue, such as adipose cell tumors, e.g., lipomas, fibrolipomas, lipoblastomas, lipomatosis, hibernomas, hemangiomas and/or liposarcomas.

In still other embodiments, the disease or pathologic condition according to the invention is a disorder characterized by aberrant cell growth of PPAR-responsive cells such as hyperplastic or neoplastic disorders of the hematopoietic system, e.g., leukemic cancers.

In another embodiment, disease or pathologic condition according to the invention is an inflammatory disease including, but not limited to, T-lymphocyte activation and other T-lymphocyte-related disorders ; inflammatory cytokine (e.g. TNF-alpha, interleukin (IL)-1-alpha, IL-1-beta, IL-2, IL-6) production ; activation of nuclear factors that promote transcription of genes encoding inflammatory cytokines.

Examples of these nuclear transcription factors include but are not restricted to, nuclear factor-kappaB (NF-kappaB), activated protein-1 (AP-1), nuclear factor of activated T cells (NFAT).

Other examples of disease or pathologic condition according to the invention are chronic viral infections (e.g. HIV, CMV, HSV, HBV, HCV infections), neurodegenerative diseases (e.g. Alzheimer's disease, multiple sclerosis, Parkinson's disease), cardiovascular disease (e.g. atherosclerosis, atherogenesis, vascular restenosis, congestive heart failure), diseases or conditions involving hypoxemia and hypoxic stress (stroke, vascular occlusive disease, MI, atherosclerosis, retinitis, retinal vein occlusion, hypoxic retinopathy, macular degeneration).

In preferred embodiment, said methods for treating and/or preventing diseases or pathologic conditions associated with cell types that express PPAR receptors are not associated with side effects, and preferably are not associated with patient weigh gain, oedema, liver toxicity, haemadilution, etc…

Alternatively, the present invention concerns a method of treating and/or preventing diseases or conditions in a patient, comprising the step of administering to said individual a pharmacologically effective dose of a compound or composition of the invention said administration resulting in improving the clinical status of said patient.

According to the present invention, the term "patient" means a mammal, e.g., a primate, e.g., a human.

By "pharmaceutically effective dose" is meant an amount of a pharmaceutical compound or composition having a therapeutically relevant effect in the frame of treatment and/or prevention of conditions mediated by PPAR, preferably PPAR-gamma. A therapeutically relevant effect relieves to some

extent one or more symptoms of conditions mediated by PPAR, preferably PPAR-gamma, in a patient or returns to normal either partially or completely one or more physiological or biochemical parameters associated with or causative of said conditions, e.g. increasing the sensitivity of cellular response to circulating insulin, curing, reducing, or preventing one or more clinical symptoms of PPAR, preferably PPAR-gamma, related conditions, including, but not limited to, hyperglycemia, hyperinsulinemia and hypertriglyceridemia. In a preferred embodiment, a pharmaceutically effective dose of a compound or composition means an amount that increases the uptake of glucose by adipose tissue or muscle tissue. In another preferred embodiment, a pharmaceutically effective dose of a compound or composition means an amount that increases the uptake of triglyceride by adipose tissue. The compounds of the invention are effective over a wide dosage range. For example, in the treatment of adult humans, dosages from about 0.05 to about 100 mg, preferably from about 0.1 to about 100 mg, per day may be used. A most preferable dosage is about 0.1 mg to about 70 mg per day. In choosing a regimen for patients it may frequently be necessary to begin with a dosage of about 2 to about 70 mg per day and when the condition is under control to reduce the dosage as low as from about 0.1 to about 10 mg per day. The exact dosage will depend upon the mode of administration, on the therapeutic effect that is intended to be achieved, the form in which the dosage is administered, the subject to be treated and the body weight of the subject to be treated, and the preference and experience of the physician or veterinarian in charge. Dosages and treatment schedules are readily attainable by routine experimentation to those having ordinary skill in this art. Generally, the compounds are dispensed in unit dosage form comprising from about 0.1 to about 100 mg of active ingredient

together with a pharmaceutically acceptable carrier per unit dosage.

The compounds or compositions of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily. Similarly, the treatment can be adapted to administer the compounds or compositions of the invention in a single weekly or monthly dose. Moreover, it will be appreciated that the amount of a compound of the invention required for use in treatment will vary with the nature of the condition being treated and the age and the condition of the patient and will be ultimately at the discretion of the attendant physician or veterinarian. In general, however, doses employed for adult human treatment will typically be in the range of 0.02 - 5000 mg per adult human per day, e.g., 1-1500 mg per adult human per day. For oral administration, the compositions are preferably provided in the form of tablets containing, 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 50.0, 100, 150, 200, 250 and 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. An effective amount of the drug is ordinarily supplied at a dosage level of from about 0.01 mg/kg to about 30 mg/kg of body weight per day. Particularly, the range is from about 0.03 to about 15 mg/kg of body weight per day, and more particularly, from about 0.05 to about 10 mg/kg of body weight per day. The compounds may be administered on a regimen of 1 to 2 times per day. Optimal dosages to be administered may be readily determined by those skilled in the art, and will vary with the particular compound used, the mode of administration, the strength of the preparation, the mode of administration, and the advancement of the disease condition. In addition, factors associated with the particular patient being treated, including patient age,

weight, diet and time of administration, will result in the need to adjust dosages.

Toxicity and therapeutic efficacy of the compounds included in the compound or composition of the invention can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD50 (the dose lethal to 50% of the population) and the ED50 (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD50/ED50. Compounds which exhibit large therapeutic indices are preferred. While compounds that exhibit toxic side effects may be used, special care should be taken to design a delivery system that targets such compounds to the site of affected tissue in order to minimize potential damage to uninfected cells and, thereby, leads to a reduction of side effects.

The data obtained from the cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED50 with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. For any compound used in the method of the invention, the therapeutically effective dose can be estimated initially from cell culture assays. A dose may be formulated in animal models to achieve a circulating plasma concentration range that includes the IC50 (i.e., the concentration of the test compound which achieves a half-maximal inhibition of symptoms) as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Levels in plasma may be measured, for example, by high performance liquid chromatography.

The route of administration of the compound or composition of the present invention may be any route, which effectively transports the active compound to the appropriate or desired site of action, such as oral, nasal, pulmonary, transdermal or parenteral e.g. rectal, depot, subcutaneous, intravenous, intraurethral, intramuscular, intranasal, ophthalmic solution or an ointment, the oral or intratumoral route being preferred.

The present invention further concerns compounds and compositions of the present invention for use in therapy. Similarly, it concerns the use of at least one compound or composition according of the present invention for the manufacture of a medicament for the treatment of diseases and conditions where modification of the effects of PPAR is of therapeutic benefit. Examples of these diseases and conditions are provided above.

According to a preferred embodiment, the present invention concerns the use of at least one compound or composition according of the present invention for the manufacture of a medicament for the treatment of individuals requiring lower blood glucose levels, i.e. for the manufacture of a medicament for lowering blood glucose levels in a patient.

According to a preferred embodiment, the present invention concerns the use of at least one compound or composition according of the present invention for the manufacture of a medicament for the treatment of individuals requiring an increased sensitivity to insulin, i.e. for the manufacture of a medicament for increasing insulin sensitivity in a patient.

The compounds and compositions of the present invention may also find use in a variety of *in vitro* and *in vivo* assays, including diagnostic assays. For example, various allotypic PPAR-gamma receptor gene expression processes may be distinguished in sensitivity assays with the subject compounds

and compositions, or panels thereof. In certain assays and in *in vivo* distribution studies, it is desirable to use labelled versions of the subject compounds and compositions, e.g. in radioligand displacement assays. Accordingly, the invention provides the compounds and compositions of the invention comprising a detectable label, which may be spectroscopic (e.g. fluorescent), radioactive, etc.

All publications and patent applications cited in this specification are herein incorporated by reference as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference. Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.

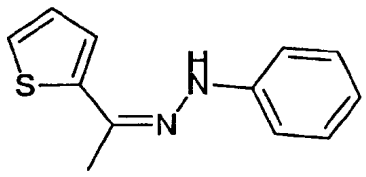
The invention has been described in an illustrative manner, and it is to be understood that the terminology which has been used is intended to be in the nature of words of description rather than of limitation. Obviously, many modifications and variations of the present invention are possible in light of the above teachings. It is therefore to be understood that within the scope of the appended claims, the invention may be practised otherwise than as specifically described. Accordingly, those skilled in the art will recognize, or able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described specifically herein. Such equivalents are intended to be encompassed in the scope of the following claims.

These and other embodiments are disclosed or are obvious from and encompassed by the description and examples of the present invention. Further literature concerning any one of the methods, uses and compounds to be employed in accordance with the present invention may be retrieved from public libraries, using for example electronic devices. For example the public database "Medline" may be utilized which is available on Internet, e.g. under http://www.ncbi.nlm.nih.gov/PubMed/medline.html. Further databases and addresses, such as http://www.ncbi.nlm.nih.gov/, http://www.infobiogen.fr/, http://www.fmi.ch/biology/research_tools.html, http://www.tigr.org/, are known to the person skilled in the art and can also be identified/located using, e.g., http://www.lycos.com. An overview of patent information in biotechnology and a survey of relevant sources of patent information useful for retrospective searching and for current awareness are given in Berks, TIBTECH 12 (1994), 352-364.

EXPERIMENTAL SECTION :

General Preparative Methods

Synthesis of Intermediate 1 : *N*-phenyl-*N'*-(1-thiophen-2-yl-ethylidene)-hydrazine



To 1-thiophen-2-yl-ethanone (1.08 ml, 9.9 mmol) in ethanol were added phenyl-hydrazine (1 ml, 9.86 mmol) and 5 drops of acetic acid. The mixture was heated at 80°C for 6 hours. The solution was evaporated to dryness, diluted in ammonium hydroxide (20 ml), filtered and washed with water to afford intermediate 1 (2.326 g, quantitative) which can be used without further purification.

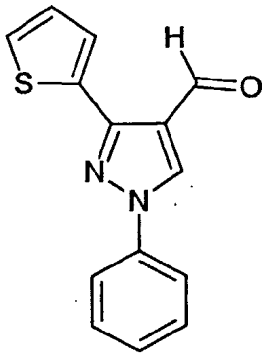
Analytical data

$C_{12}H_{12}N_2S$

MM: 216.31 $g.mol^{-1}$

Mp : 96.4 - 97.5°C

Synthesis of Intermediate 2 : 1-phenyl-3-thiophen-2-yl-1H-pyrazole-4-carbaldehyde



A solution of phosphorus oxychloride (0.86 ml, 9.23 mmol) was added drop wise to a well stirred solution of DMF (2.2 ml) under argon at 0°C. The mixture was stirred between 0 and 10°C for 0.5 hour. A solution of intermediate 1 (1 g, 4.62 mmol) in DMF (1.7 ml) was slowly added over 10 minutes to maintain the temperature between 0 and 10°C. The reaction was stirred an additional 1 hour at this temperature and then an additional 2 hours at 60°C. The mixture was cooled and neutralized with sodium carbonate to pH=8. The precipitate was filtered, washed with water and recrystallized from methylene chloride to obtain a beige solid (878 mg, 75%).

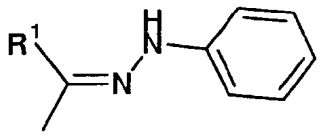
Analytical data

$C_{14}H_{10}N_2OS$

MM: 254.31 $g.mol^{-1}$

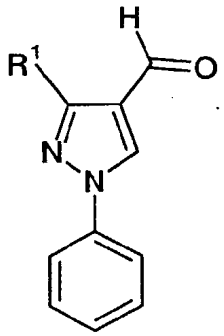
Mp : 98.3 - 98.7°C (lit. 94°C)

Synthesis of Intermediate 3 : *N*-phenyl-*N'*-[(1-aryl(heteryl))-ethylidene]-hydrazine



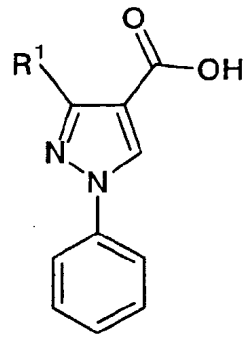
To a solution of the aryl methyl ketone (R^1-CO-CH_3) (1 eq) in ethanol were added phenyl-hydrazine (1 eq) and 5 drops of acetic acid. The reaction was heated at 80°C for 6 hours, then the solution was evaporated to dryness, diluted in ammonium hydroxide, filtered and washed with water to produce intermediate 3 (quantitative) which can be used without further purification.

Synthesis of Intermediate 4 : 1-phenyl-3-aryl(heteryl)-1H-pyrazole-4-carbaldehyde



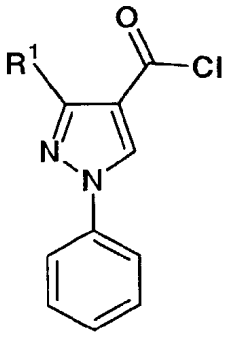
A solution of phosphorus oxychloride (0.86 ml, 9.23 mmol) was added drop wise to a well stirred solution of DMF (2.2 ml) under argon at 0°C. The mixture was stirred between 0 and 10°C for 0.5 hour. A solution of intermediate 3 (4.62 mmol) in DMF (1.7 ml) was slowly added over 10 minutes to maintain the temperature between 0 and 10°C. The reaction was stirred an additional 1 hour at this temperature and then an additional 2 hours at 60°C. The mixture was cooled and neutralized with sodium carbonate to pH=8. The precipitate was filtered, washed with water and recrystallized from methylene chloride.

Synthesis of Intermediate 5 : 1-phenyl-3-aryl(heteryl)-1H-pyrazole-4-carboxylic acid



To a stirred suspension of 50 mmol of intermediate 4 in 50 ml of 50% aqueous pyridine cooled in a water bath, is added in small portions potassium permanganate (7.9 g, 50 mmol) over 1 hour while maintaining the temperature of the reaction at 20°C. After the addition is complete, the mixture was stirred till the violet color disappeared. The manganese dioxide precipitate is filtered, washed with 5% sodium hydroxide, and to the filtrate is added diluted hydrochloric acid. The desired carboxylic acid which precipitates is filtered, dried and recrystallized from glacial acetic acid.

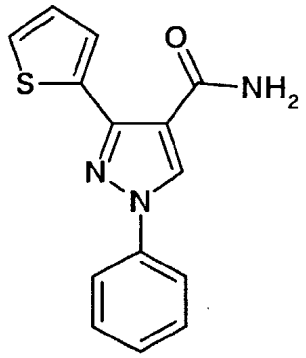
Synthesis of Intermediate 6 : 1-phenyl-3-aryl(heteryl)-1H-pyrazole-4-carbonyl chloride



To a suspension of intermediate 5 (2 mmol) in anhydrous toluene (15 ml) were added thionyl chloride (50 mmol) and 3-4 drops of dimethylformamide. The mixture was heated to 110°C for 2 hours and then the excess of thionyl chloride and

solvent are removed under vacuum. The residue was washed with hexane and crystallized from a mixture toluene-hexane (3:1).

Synthesis of Intermediate 7 : 1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid amide.



To a solution of intermediate 5 (R^1= thienyl, 7 g; 24.3 mmol) in anhydrous THF (35 ml) is bubbled ammoniac gaz during 30 minutes. The mixture was stirred over night at room temperature. The product was extracted with CH_2Cl_2, washed with water and dried over Na_2SO_4. The product was concentrated under reduced pressure to produce (5.6 g; 86 %) the desired product.

Analytical data

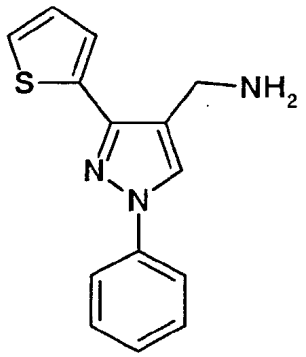
$C_{14}H_{11}N_3OS$

MM: 269.33 $g.mol^{-1}$

MS (ESI+): 270;(ESI-): 268

RMN ^1H (400Mhz, $CDCl_3$) δ (ppm) : 5.85 (br, 2H, NH_2), 7.18 (dd, 1H, J_1= 3.52, J_2 = 5.1, H), 7.39 (t, 1H, J = 7.44, H_{arom}), 7.48-7.51 (m, 3H, H_{arom}), 7.59 (s, 1H, H_{arom}), 7.77 (d, 2H, J = 8.2, H_{arom}), 8.53 (s, 1H, $H_{pyrazole}$)

Synthesis of Intermediate 8 : C-(1-Phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-methylamine.



To a solution of intermediate 7 (5 g; 18.1 mmol) in anhydrous THF (40 ml) under argon atmosphere at 0°C iwas added a solution of $LiAlH_4$ in THF (90 ml; 1 mmol/l). The mixture was heated at reflux for 3 hours and then cooled in ice. The reaction was hydrolyzed with 0.7 ml of H_2O, 0.7 ml of NaOH (15%), followed by another 2 ml of H_2O. The gel is removed by filtration and the filtrate concentrated under reduced pressure to afford 7 g of an oil. To a solution of the oil in anhydrous CH_2Cl_2 (10 ml) is bubbled HCl gaz during 5 minutes. The precipitate was filtered, washed with CH_2Cl_2 and dried to afford (4.0 g; 76 %) of the hydrochloride salt of the desired product.

Analytical data

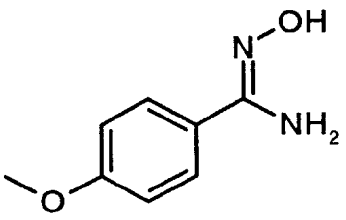
$C_{14}H_{13}N_3S$

MM: 255.34 $g.mol^{-1}$

MS (ESI+): 256; (ESI-): 254

RMN ^1H (400Mhz, $CDCl_3$) δ (ppm) : 4.9 (s, 2H, CH_2), 7.02-7.60 (m, 6H, H_{arom}), 7.79-7.91 (m, 2H, H_{arom}), 8.55 (s, 1H, $H_{pyrazole}$).

Synthesis of Intermediate 9 : N-Hydroxy-4-methoxy-benzamidine



A solution of 4-methoxybenzonitrile (2.0 g, 15 mmol, 1 eq) and hydroxylamine 50wt% solution (0.92 ml, 15 mmol, 1 eq) in ethanol (16 mL) was heated to reflux overnight. EtOH was evaporated and the residu was dissolved in EtOAc and washed with water, dried, filtered and the solvent evaporated to give the product (1.9g, 76%) as a white solid.

Analytical data

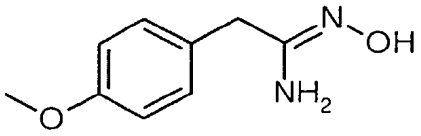
$C_8H_{10}N_2O_2$

MM: 166.18 $g.mol^{-1}$

MS (ESI+): 167

Mp: 114-115°C

Synthesis of Intermediate 10 : N-Hydroxy-2-(4-methoxy-phenyl)-acetamidine



A solution of (4-methoxyphenyl)acetonitrile (1.0 g, 6.8 mmol, 1 eq) and hydroxylamine 50wt% solution (0.42 ml, 6.8 mmol, 1 eq) in ethanol (5 mL) was heated to reflux for 4 hours. EtOH was evaporated and the residu was dissolved in EtOAc and washed with water, dried, filtered and the solvent evaporated to give the product (1.03g, 84%) as a white solid.

Analytical data

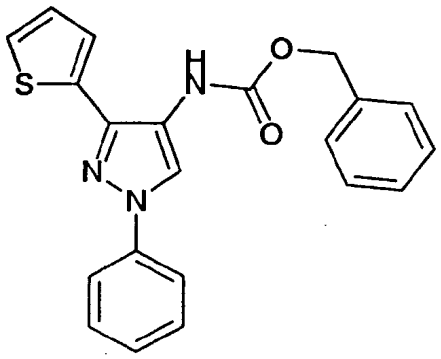
$C_9H_{12}N_2O_2$

MM: 180.21 $g.mol^{-1}$

MS (ESI+): 181

Mp: 108-109°C

Synthesis of Intermediate 11 : (1-Phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-carbamic acid benzyl ester (CRX000382)



To a solution of intermediate 5 (R^1=thiophene)(1 g, 3.7 mmol) in toluene (15 ml) was added triethylamine (0.62 ml, 4.44 mmol) and diphenylphosphinoazide (0.92 ml, 4.23 mmol). The mixture was heated at 85°C for 3 hours and cooled to room temperature, the benzyl alcohol (0.46 mmol, 4.44 mmol) was added, and the mixture was heated at 85°C for an additional 19 hours. The solvent was evaporated and the residu was dissolved in EtOAc and washed with a solution of $NaHCO_3$, water, dried, filtered and the solvent evaporated. The residue was purified by flash column chromatography (Heptane/AcOEt, 8/2) to afford a brown solid (600 mg; 43%).

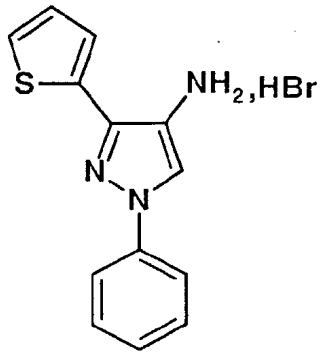
Analytical data

$C_{21}H_{17}N_3O_2S$

MM: 375.45 $g.mol^{-1}$

MS (ESI+): $(2M+H)^+$ = 751

Synthesis of Intermediate 12 : 1-Phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylamine (CRX000301)



To a solution of intermediate 11 (4.18 g, 11.1 mmol) in dichloromethane (15 ml) was added a solution (40ml) of HBr (45

%) in acetic acid. The mixture was stirred at room temperature for 3 days. The solvent was evaporated and the solid was filtered, washed with dichloromethane and dried (3.44g, 96 %).

Analytical data

$C_{13}H_{11}N_3S$

MM : 241.32 $g.mol^{-1}$

MS (ESI+): $(M+MeCN+H)^+$ = 284

Example 1

Preparation of 2-(1-Phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethylene)-indan-1-one (CRX000470)

To a solution of intermediate 2 (800 mg, 3.15 mmol) in 10 ml of 2-propanol was added indanone (416 mg, 3.15 mmol) while stirring at room temperature. The reaction mixture was heated to 50°C, and 0.71 ml of 20% aqueous sodium hydroxide was added. The mixture was stirred at 50°C for 0.5 hour, cooled to room temperature and stirred for an additional 3 hours. The precipitate was filtered off and crystallized from 2-propanol to produce 2-(1-Phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethylene)-indan-1-one (200 mg, 55%) as a white solid.

Analytical data

$C_{23}H_{16}N_2OS$

MM: 368.46 $g.mol^{-1}$

MS (ESI+): 369

Mp: 204-206°C.

Example 2

Preparation of 5-Methoxy-2-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethylene)-indan-1-one (CRX000405)

To a solution of intermediate 2 (500 mg, 1.97 mmol) in 4 ml of 2-propanol was added 5-methoxy-indanone (320 mg, 1.97 mmol) while stirring at room temperature. The reaction mixture was heated to 50°C, and 0.44 ml of 20% aqueous sodium hydroxide was added. The mixture was stirred at 50°C for 0.5

hour, cooled to room temperature and stirred for an additional 3 hours. The precipitate was filtered off and crystallized from 2-propanol to produce 5-Methoxy-2-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethylene)-indan-1-one (300 mg, 38%) as a yellow solid.

Analytical data

$C_{24}H_{18}N_2O_2S$

MM: 398.49 $g.mol^{-1}$

MS (ESI+): 399

RMN ^1H (400Mhz, $CDCl_3$) δ (ppm) : 3.75 (s, 2H, CH_2), 3.83 (s, 3H, MeO), 6.93-6.95 (dd, 1H, J_1 = 1.76, J_2 = 8.5, H_{arom}), 6.99 (s, 1H, H) 7.17-7.19 (t, 1 H, J = 4.4, H), 7.36-7.4 (t, 1H, J = 7.32, H), 7.43 (d, 1H, J = 5, H_{arom}), 7.48 (d, 1H, J = 3.5, H_{arom}), 7.5-7.55 (t, 2H, J = 7.6, H), 7.81-7.83 (m, 4H, , H_{arom}), 8.2 (s, 1H, $H_{pyrazole}$).

Example 3

Preparation of 6-Methoxy-2-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethylene)-3,4-dihydro-2H-naphthalen-1-one (CRX000366)

To a solution of intermediate 2 (300 mg, 1.18 mmol) in 3 ml of 2-propanol was added 6-methoxy-1-tetralone (208 mg, 1.18 mmol) while stirring at room temperature. The reaction mixture was heated to 50°C, and 0.27 ml of 20% aqueous sodium hydroxide was added. The mixture was stirred at 50°C for 0.5 hour, cooled to room temperature and stirred for an additional 3 hours. The precipitate was filtered off and crystallized from 2-propanol to produce 6-Methoxy-2-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethylene)-3,4-dihydro-2H-naphthalen-1-one (250 mg, 51%) as a yellow solid.

Analytical data

$C_{25}H_{20}N_2O_2S$

MM: 412.51 $g.mol^{-1}$

Mp : 154-156°C

RMN ^1H (400Mhz, $CDCl_3$) δ (ppm) : 2.99-3.03 (t, 2H, J = 6.16 , CH_2-CH_2-Ph), 3.11-3.14 (t, 2H, J = 5.6, CH_2-CH_2-Ph), 3.88 (s, 3H, MeO), 6.76 (d, 1H, J = 2.32, H_1), 6.90-6.93 (dd, 1H, J_1 = 2.36, J_2 = 8.80, H), 7.14 (dd, 1H, J_1 = 3.8, J_2 = 5, H), 7.35-7.4 (m, 2H, H_{arom}), 7.45 (dd, 1H, J_1 = 1, J_2 = 3.5, H_{arom}), 7.5-7.54 (t, 2H, J = 7.5, H), 7.82(m, 2H, H_{arom}), 7.98 (s, 1H, $H_{ethylenique}$), 8.1 (s, 1H, $H_{pyrazole}$), 8.15 (d, 1H, J_1 = 8.1, H_{arom}).

Example 4

Preparation of 2-(1-Phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethyl)-isoindole-1,3-dione (CRX000466)

To a solution of intermediate 8 (400 mg, 1.57 mmol) and phtalic anhydride (140 mg, 0.94 mmol) in 2.7 ml of acetic acid were added sodium acetate (167 mg, 2.0 mmol) and acetic acid (1 ml). The mixture was heated to reflux for 2 hours, and additionally stirred overnight at room temperature. The mixture was filtered to produce 2-(1-Phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethyl)-isoindole-1,3-dione (64 mg, 18%) as a yellow solid.

Analytical data

$C_{22}H_{15}N_3O_2S$

MM: 385.45 $g.mol^{-1}$

MS (ESI+): 386

Mp : 170-171°C.

Example 5

Preparation of 1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (1H-indazol-5-yl)-amide (CRX000175)

To a solution of intermediate 6 (R^1=2-thienyl) (200 mg; 0.73 mmol) in toluene (10 ml) while stirring were added the amine (1H-Indazol-5-ylamine) (200 mg; 0.73 mmol) and triethylamine (0.4 ml). The mixture was heated to 110°C for 3 hours then cooled to room temperature and left standing for 12 hours. The solvent was evaporated, the residue was treated

with water, filtered, dried. The residue was purified by flash column chromatography (Heptane/AcOEt, 7/3) to afford 1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (1H-indazol-5-yl)-amide (120 mg, 31 %) as a purple solid.

Analytical data

$C_{21}H_{15}N_5OS$

MM: 385.45 $g.mol^{-1}$

MS (ESI+): 386

Mp : 212°C.

Example 6

Preparation of 5-Methoxy-2-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethyl)-indan-1-one (CRX000440)

To a solution of example 2 (200 mg, 0.5 mmol) in 4 ml of absolute ethanol was added Palladium of carbon (20 mg). The suspension was stirred under H_2 (5 atm.) at room temperature for 18 hours. The reaction mixture was filtered through celite. The filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography (Heptane/AcOEt, 8/2) to afford 5-Methoxy-2-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethyl)-indan-1-one as a yellow solid (80 mg, 40%).

Analytical data

$C_{24}H_{20}N_2O_2S$

MM: 400.50 $g.mol^{-1}$

MS (ESI+): 401.

Example 7

Preparation of 6-Methoxy-2-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethyl)-3,4-dihydro-2H-naphthalen-1-one (CRX000439)

To a solution of example 3 (200 mg, 0.49 mmol) in 4 ml of absolute ethanol was added Palladium of charbon (20 mg). The

suspension was stirred under H_2 (10 atm.) at room temperature for 18 hours. The reaction mixture was filtered through celite. The filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography (Heptane/AcOEt, 8/2) to afford 6-Methoxy-2-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethyl)-3,4-dihydro-2H-naphthalen-1-one as a yellow solid (34 mg, 17%).

Analytical data

$C_{25}H_{22}N_2O_2S$

MM: 414.53 $g.mol^{-1}$

MS (ESI+): 415.

Example 8

Preparation of 5-Methoxy-2-(1-phenyl-3-pyridin-3-yl-1H-pyrazol-4-ylmethylene)-indan-1-one (CRX000445)

To a solution of intermediate 4 (R^1 = pyridin-3-yl) (500 mg, 2 mmol) in 3 ml of 2-propanol was added 5-methoxy-1-indanone (325 mg, 2 mmol) while stirring at room temperature. The reaction mixture was heated to 50°C, and 0.45 ml of 20% aqueous sodium hydroxide was added. The mixture was stirred at 50°C for 0.5 hour then cooled to room temperature and stirred for an additional 3 hours. The separated precipitate was filtered off and crystallized from 2-propanol to afford 5-Methoxy-2-(1-phenyl-3-pyridin-3-yl-1H-pyrazol-4-ylmethylene)-indan-1-one (150 mg, 20%) as a yellow solid.

Analytical data

$C_{25}H_{19}N_3O_2$

MM: 393.45 $g.mol^{-1}$

MS (ESI+): 394

Mp : 212-213°C.

Example 9

Preparation of 3-(4-Methoxy-phenyl)-5-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-[1,2,4]oxadiazole (CRX000459)

A solution of intermediate 6 (200 mg, 0.69 mmol, 1 eq) and intermediate 9 (115 mg, 0.69 mmol, 1 eq) in dioxane (10 mL) was heated to 100°C for 20 hours. Dioxane was evaporated. The residu was dissolved in EtOAc and washed with water, dried, filtered and the solvent evaporated to give a product which was triturated in ether, filtered and dried. The 3-(4-Methoxy-phenyl)-5-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-[1,2,4]oxadiazole was obtained as a brown solid (138 mg, 50%).

Analytical data

$C_{22}H_{16}N_4O_2S$

MM: 400.46 $g.mol^{-1}$

Mp: 182-183°C

NMR 1H (DMSO): 9.50 (s, 1H); 8.20 (s, 1H); 7.98 (d, 2H); 7.66 (d, 2H); 7.64 (t, 2H); 7.46 (t, 1H); 7.19 (m, 1H); 7.05 (d, 2H); 6.91 (bs, 1H); 3.84 (s, 3H).

Example 10

Preparation of 3-(4-Methoxy-benzyl)-5-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-[1,2,4]oxadiazole (CRX000513)

A solution of intermediate 6 (300 mg, 1.04 mmol, 1 eq) and intermediate 10 (187 mg, 1.04 mmol, 1 eq) in dioxane (12 mL) was heated to 100°C for 12 hours. Dioxane was evaporated. The residu was dissolved in THF (5 mL) and Et_3N (0.14 mL, 1.04 mmol, 1eq) and nBu_4NF 1M in THF 1.04 mL, 1.04 mmol, 1eq.) was added. The solution was stirred at room temperature for 12 hours before being washed with water and extracted with EtOAc; The organic layer was dried, filtered and concentrated to give the 3-(4-Methoxy-benzyl)-5-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-[1,2,4]oxadiazole as a brown solid (50 mg, 12%).

Analytical data

$C_{23}H_{18}N_4O_2S$

MM: 414.49 $g.mol^{-1}$

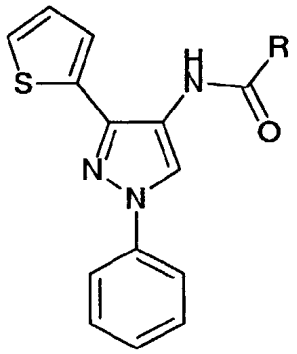
LC: 96%

Mp: 182-183°C

NMR 1H (DMSO): 8.61 (s, 1H); 8.24 (d, 1H); 7.78 (dd, 2H); 7.50 (t, 2H); 7.36 (m, 3H); 7.25 (s, 1H); 7.12 (dd, 1H); 6.73 (m, 2H); 4.09 (s, 2H); 3.79 (s, 3H).

Example 11

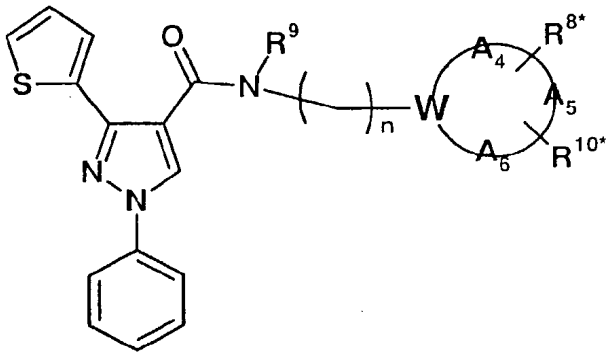
General procedure 1 (GP1): « RETRO-AMIDE R = non-cyclic»



To a solution of intermediate 12 (46 mg, 0.143 mmol) in dichloromethane (6 ml) while stirring were added the "reactant" carboxylic acid (RCOOH) (0.143 mmol, 1 eq), EDCI (30 mg, 0.16 mmol), and dimethylaminopyridine (23 mg, 0.16 mmol). The mixture was heated to 65°C for 1.5 hours then cooled to room temperature and left standing for 18 hours. The mixture was washed with water and the solvent was evaporated. The solid was washed with Et_2O and dried to afford a solid.

Example 12

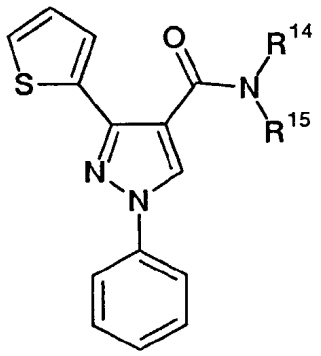
General procedure 2 (GP2): « AMIDE cyclic» : Preparation of 1-phenyl-3-thiophenyl-1H-pyrazole-4-carboxamide



To a solution of intermediate 6 (R^1=thiophene) (2.5 mmol) in toluene (10 ml) while stirring were added the "reactant" amine (mono or bi-cyclic carbo or hetero ring) (2.5 mmol) and triethylamine (0.4 ml). The mixture was heated to 110°C for 3 hours then cooled to room temperature and left standing for 12 hours. The solvent was evaporated, the residue was treated with water, filtered, dried, and crystallized from an appropriate solvent.

Example 13

General procedure 3 (GP3): « AMIDE non-cyclic» - Preparation of 1-phenyl-3-thiophenyl-1H-pyrazole-4-carboxamide

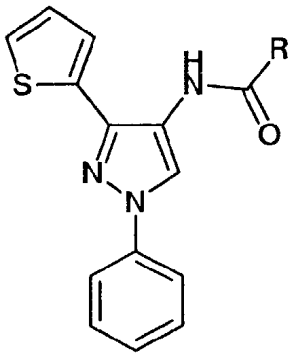


To a solution of intermediate 6 (R^1=thiophene) (2.5 mmol) in toluene (10 ml) while stirring were added the "reactant" amine ($NHR^{14}R^{15}$) (2.5 mmol) and triethylamine (0.4 ml). The mixture was heated to 110°C for 3 hours then cooled to room

temperature and left standing for 12 hours. The solvent was evaporated, and the residue was treated with water, filtered, dried, and crystallized from an appropriate solvent.

Example 14

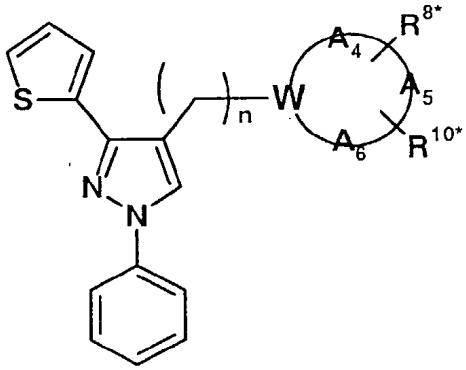
General procedure 4 (GP4): « RETRO-AMIDE R = cyclic»



To a solution of intermediate 12 (46 mg, 0.143 mmol) in dichloromethane (6 ml) while stirring were added the "reactant" carboxylic acid (RCOOH)(0.143 mmol, 1 eq), EDCI (30 mg, 0.16 mmol), and dimethylaminopyridine (23 mg, 0.16 mmol). The mixture was heated to 65°C for 1.5 hours then cooled to room temperature and left standing for 18 hours. The mixture was washed with water and the solvent was evaporated. The solid was washed with Et_2O and dried to afford a solid.

Example 15

General procedure 5 (GP5): « AMINE III cyclic»

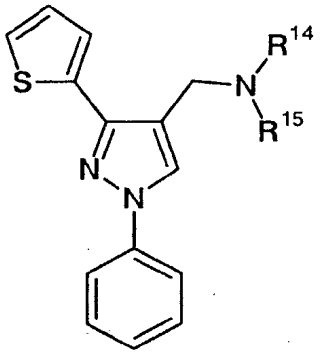


To a solution of intermediate 2 (2.0 mmol) in methanol (10 ml) while stirring were added the "reactant" amine (mono

or bi-cyclic carbo or hetero ring) (3.0 mmol), diisopropylethylamine (1.1 ml, 6.3 mmol) and sodium sulfate (300 mg). The mixture was heated to reflux for one hour then cooled to room temperature and sodium cyanoborohydride (136 mg, 2.2 mmol) was added. The mixture was left standing for 18 hours. The solid was filtered and the solvent was evaporated. The residue was treated with ethyl acetate, washed with water, dried, and evaporated. The product was purified by flash chromatography.

Example 16

General procedure 6 (GP6): « AMINE III non cyclic»



To a solution of intermediate 2 (2.0 mmol) in methanol (10 ml) while stirring are added the "reactant" amine ($NHR^{14}R^{15}$) (3.0 mmol), diisopropylethylamine (1.1 ml, 6.3 mmol) and sodium sulfate (300 mg). The mixture was heated to reflux for one hour then cooled to room temperature and sodium cyanoborohydride (136 mg, 2.2 mmol) was added. The mixture was left standing for 18 hours. The solid was filtered and the solvent was evaporated. The residue was treated with ethyl acetate, washed with water, dried, and evaporated. The product was purified by flash chromatography.

Examples 17-90

The following compounds have been prepared according to the above described General procedures GP1-GP6, using the mentioned "reactant".

General procedure	"Reactant" Name	Corporate ID	Compound of the Invention	LCMS ESI + : $(M+H)^+$
GP4	(1-Methyl-1H-indol-3-yl)-acetic acid	CRX000339	2-(1-Methyl-1H-indol-3-yl)-N-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-acetamide	413
GP4	Benzo[1,3]dioxole-4-carboxylic acid	CRX000329	Benzo[1,3]dioxole-4-carboxylic acid (1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-amide	390
GP4	Naphthalen-1-yl-acetic acid	CRX000330	2-Naphthalen-1-yl-N-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-acetamide	410
GP2	Isoxazol-3-ylamine	CRX000238	1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid isoxazol-3-ylamide	337
GP2	2,5-Dimethyl-2H-pyrazol-3-ylamine	CRX000376	1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (2,5-dimethyl-2H-pyrazol-3-yl)-amide	364

GP2	3-Methyl-isothiazol-5-ylamine	CRX000241	1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (3-methyl-isothiazol-5-yl)-amide	367
GP2	2-Ethyl-2H-pyrazol-3-ylamine	CRX000148	1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (2-ethyl-2H-pyrazol-3-yl)-amide	364
GP2	4-Methoxy-6-methyl-pyrimidin-2-ylamine	CRX000260	1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (4-methoxy-6-methyl-pyrimidin-2-yl)-amide	392
GP2	2-Amino-thiazol-4-one	CRX000244	1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (4-oxo-4,5-dihydro-thiazol-2-yl)-amide	369
GP2	1H-[1,2,4]Triazol-3-ylamine	CRX000354	1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (1H-[1,2,4]triazol-3-yl)-amide	$(M+MeCN+H)^+$ = 378

GP2	C-Thiophen-2-yl-methylamine	CRX000243	1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (thiophen-2-ylmethyl)-amide	366
GP2	C-(5-Methyl-furan-2-yl)-methylamine	CRX000265	1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (5-methyl-furan-2-ylmethyl)-amide	364
GP2	C-Furan-2-yl-methylamine	CRX000221	1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (furan-2-ylmethyl)-amide	350
GP2	3,4-Dimethyl-isoxazol-5-ylamine	CRX000266	1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (3,4-dimethyl-isoxazol-5-yl)-amide	365
GP2	1H-Tetrazol-5-ylamine	CRX000177	1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (1H-tetrazol-5-yl)-amide	$(2M+H)^+ = 675$
GP2	C-Pyridin-4-yl-methylamine	CRX000194	1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (pyridin-4-ylmethyl)-amide	361

GP2	C-Pyridin-3-yl-methylamine	CRX000267	1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (pyridin-3-ylmethyl)-amide	361
GP2	C-Pyridin-2-yl-methylamine	CRX000242	1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (pyridin-2-ylmethyl)-amide	361
GP2	Pyridin-2-ylamine	CRX000355	1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid pyridin-2-ylamide	347
GP2	Pyridin-3-ylamine	CRX000356	1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid pyridin-3-ylamide	347
GP2	Pyridin-4-ylamine	CRX000187	1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid pyridin-4-ylamide	347
GP2	1-Benzyl-piperidin-4-ylamine	CRX000153	1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (1-benzyl-piperidin-4-yl)-amide	443

GP2	2-Morpholin-4-yl-ethylamine	CRX000154	1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (2-morpholin-4-yl-ethyl)-amide	383
GP2	1-Piperazin-1-yl-ethanone	CRX000161	1-[4-(1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carbonyl)-piperazin-1-yl]-ethanone	381
GP2	1,2,3,4-Tetrahydro-quinoline	CRX000162	(3,4-Dihydro-2H-quinolin-1-yl)-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-methanone	386
GP2	Piperidine	CRX000164	(1-Phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-piperidin-1-yl-methanone	338
GP2	Morpholine	CRX000166	Morpholin-4-yl-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-methanone	340
GP2	4-Methyl-piperidine	CRX000170	4-Methyl-piperidin-1-yl)-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-methanone	352
GP2	1H-Indazol-5-ylamine	CRX000175	1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (1H-indazol-5-yl)-amide	386

GP2	C-Naphthalen-1-yl-methylamine	CRX000193	1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (naphthalen-1-ylmethyl)-amide	410
GP2	C-Benzo[1,3]dioxol-5-yl-methylamine	CRX000202	1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)-amide	404
GP2	Naphthalen-2-ylamine	CRX000204	1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid naphthalen-2-ylamide	396
GP2	Indan-5-ylamine	CRX000219	1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid indan-5-ylamide	386
GP2	1-Phenyl-piperazine	CRX000222	(4-Phenyl-piperazin-1-yl)-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-methanone	415
GP2	1-(4-Piperazin-1-yl-phenyl)-ethanone	CRX000223	1-{4-[4-(1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carbonyl)-piperazin-1-yl]-phenyl}-ethanone	457

GP2	1-Pyridin-2-yl-piperazine	CRX000224	(1-Phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-(4-pyridin-2-yl-piperazin-1-yl)-methanone	416
GP2	1,2,3,4-Tetrahydro-isoquinoline	CRX000225	(3,4-Dihydro-1H-isoquinolin-2-yl)-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-methanone	386
GP2	1-Benzyl-piperazine	CRX000226	(4-Benzyl-piperazin-1-yl)-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-methanone	429
GP2	1-(4-Methoxy-phenyl)-piperazine	CRX000227	[4-(4-Methoxy-phenyl)-piperazin-1-yl]-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-methanone	445
GP2	1H-Indol-5-ylamine	CRX000258	1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (1H-indol-5-yl)-amide	385
GP2	1-(3-Methoxy-phenyl)-piperazine	CRX000269	4-(4-Methoxy-phenyl)-piperazin-1-yl]-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-methanone	445

GP5	Morpholine	CRX000299	4-(1-Phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethyl)-morpholine	326
GP5	4-Methyl-piperidine	CRX000300	4-Methyl-1-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethyl)-piperidine	338
GP2	4-Benzyl-piperidine	CRX000307	(4-Benzyl-piperidin-1-yl)-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-methanone	$(2M+H)^+ = 855$
GP2	5-Amino-2-methyl-isoindole-1,3-dione	CRX000309	1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (2-methyl-1,3-dioxo-2,3-dihydro-1H-isoindol-5-l)-amide	429
GP2	Furan-2-ylmethyl-methyl-amine	CRX000311	1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid furan-2-ylmethyl-methyl-amide	364
GP4	Pyridine-3-carboxylic acid	CRX000328	N-(1-Phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-nicotinamide	$(M+MeCN+H)^+ = 388$
GP4	Pyridine-4-carboxylic acid	CRX000333	N-(1-Phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-isonicotinamide	$(M+MeCN+H)^+ = 388$

GP4	Pyridine-2-carboxylic acid	CRX000334	Pyridine-2-carboxylic acid (1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-amide	347
GP5	1-Piperazin-1-yl-ethanone	CRX000341	1-[4-(1-Phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethyl)-piperazin-1-yl]-ethanone	367
GP5	Piperidine	CRX000343	1-(1-Phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethyl)-piperidine	360
GP5	1-Benzyl-piperazine	CRX000352	1-Benzyl-4-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethyl)-piperazine	415
GP4	1-Methyl-1H-indole-3- carboxylic acid	CRX000377	1-Methyl-1H-indole-3-carboxylic acid (1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-amide	399
GP2	Methyl-pyridin-2-yl-amine	CRX000381	1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid methyl-pyridin-2-yl-amide	361
GP4	Thiophene-2-carboxylic acid	CRX000393	Thiophene-2-carboxylic acid (1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-amide	ESI - : $(M-H^+)^-$ = 350

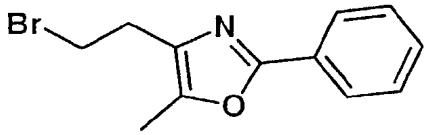
GP4	1-Acetyl-piperidine-4- carboxylic acid	CRX000400	1-Acetyl-piperidine-4-carboxylic acid (1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-amide	395
GP5	1-Benzo[1,3]dioxol-5-ylmethyl-piperazine	CRX000403	1-Benzo[1,3]dioxol-5-ylmethyl-4-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethyl)-piperazine	419
GP5	1-(4-Piperazin-1-yl-phenyl)-ethanone	CRX000438	1-(4-Isopropyl-phenyl)-4-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethyl)-piperazine	445
GP3	Butylamine	CRX000191	1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid butylamide	326
GP3	N-(2-Amino-ethyl)-acetamide	CRX000217	1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (2-acetylamino-ethyl)-amide	355
GP3	Ethylamine	CRX000239	1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid ethylamide	298

GP3	2-Amino-acetamide	CRX000240	1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (2-oxo-propyl)-amide	327
GP3	N-(4-Amino-butyl)-acetamide	CRX000257	1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid [4-(2-oxo-propylamino)-butyl]-amide	383
GP3	2-Methoxy-ethylamine	CRX000262	1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (2-methoxy-ethyl)-amide	328
GP3	Diethyl-amine	CRX000268	1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid diethylamide	326
GP6	Diethyl-amine	CRX000279	Diethyl-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethyl)-amine	312
GP3	N,N,N'-Trimethyl-ethane-1,2-diamine	CRX000298	1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (3-dimethylamino-propyl)-methyl-amide	355
GP3	Dibenzyl-amine	CRX000306	1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid	450

			dibenzylamide	
GP3	Dimethyl-amine	CRX000310	1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid dimethylamide	298
GP3	Methyl-propyl-amine	CRX000312	1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid methyl-propyl-amide	326
GP3	N,N,N'-Trimethyl-propane-1,3-diamine	CRX000340	1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (3-dimethylamino-propyl)-methyl-amide	369
GP6	Methyl-propyl-amine	CRX000353	Methyl-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethyl)-propyl-amine	312
GP3	Diisopropyl-amine	CRX000397	1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid diisopropylamide	354
GP1	Acetylamino-acetic acid	CRX000399	2-Acetylamino-N-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-acetamide	341

EXAMPLE 91 : Synthesis of 5-Methyl-2-phenyl-4-[3-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-allyl]-oxazole [CRX000783]

- **Intermediate 13 : 4-(2-Bromo-ethyl)-5-methyl-2-phenyl-oxazole**



To a well stirred solution of 2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethanol (5.0 g, 24.6 mmol and CBr_4 (12.2 g, 36.9 mmol) in CH_2Cl_2 (50 ml) under argon at r.t., was added dropwise a solution of triphenylphosphine (6.4 g, 24.6 mmol) in CH_2Cl_2 (30 ml). The mixture was stirred at r.t. overnight. The solution was washed with K_2CO_3 aq. sat., H_2O and brine, dried over Na_2SO_4 and evaporated to dryness. the residu was purified by flash chromatography on silica gel (EtOAc/Heptane 2:8) to give the product as a white solid (6.0 g, 92%).

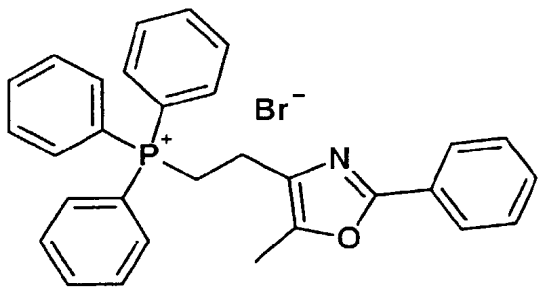
Analytical data

$C_{12}H_{12}BrNO$

MM: 266.14 $g.mol^{-1}$

MS : 266

- **Intermediate 14 : [2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethyl]-triphenyl-phosphonium bromide**

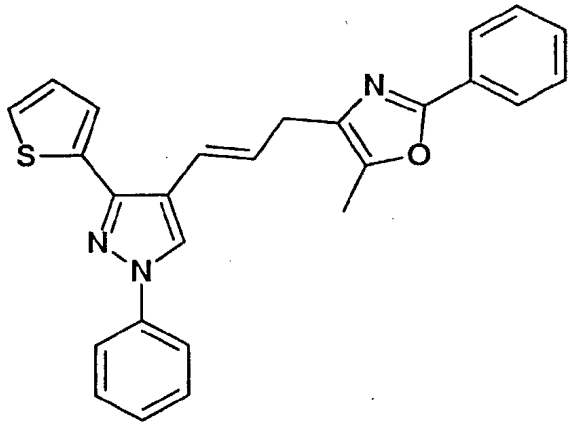


A solution of triphenylphosphine (21 g, 81 mmol) and Intermediate 13 (4.3 g, 16.15 mmol) in anhydrous acetonitrile

(100 mL) was heated to reflux and stirred overnight. The solvent was evaporated and the residu filtered and washed several times with diethylether.

Due to its apparently high hygroscopy, the white solid (8.38 g, 98 %) is rapidly used "as is" in the next step.

- **Synthesis of 5-Methyl-2-phenyl-4-[3-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-allyl]-oxazole [CRX000783]**



To a solution of the reactant "phosphonium salt" intermediate 14 (ph. Int.) (600 mg, 1.14 mmol) in 4 mL anhydrous methanol was added a 0.5 M solution of MeONa in methanol (2.4 ml, 1.20 mmol). After stirring during 20 minutes at room temperature under inert atmosphere, the mixture was condensed to dryness, twice coevaporated with toluene (2.5 ml) and suspended in 5 mL toluene.

To this suspension, the reactant "aldehyde" intermediate 2 (ald. Int.)(144 mg, 0.57 mmol) was added directly as a powder. After stirring overnight at 110 °C, the mixture was concentrated and purified by flash chromatography on silica gel (Ethyl acetate 3 : Heptane 7) to give the product as a mixture of the cis and trans isomers (trans isomer 86.6%).

Analytical data

$C_{26}H_{21}N_3OS$

MM: 423.54 $g.mol^{-1}$

MS (ESI+) : 424

Material

Plasmids :

- GAL4-hPPAR-gamma LBD plasmid : expression vector encoding a chimeric construct comprising the GAL4 DBD (DNA Binding Domain) and the human PPAR-gamma LBD ;

- luciferase reporter plasmid : vector in which luciferase gene expression is placed under the control of a GAL4 response element ;

- pCMV-betaGAL plasmid: control of transfection efficiency, it is a vector encoding the beta-galactosidase gene.

Rosiglitazone: Rosiglitazone is a high affinity PPAR-gamma ligand (Lehmann, et al., 1995, J. Biol. Chem. 270, 12953-12956) and is a member of the thiazolidinedione class of compounds. Rosiglitazone possesses the capacity to activate PPAR-gamma *in vitro* during transfection assays, to induce adipogenesis both *in vitro* and *in vivo* (Fajas et al., 1998; Curr. Opin. Cell Biol. 10, 165-173 ; Spiegelman, 1998, Diabetes 47, 507-514), and to improve insulin sensitivity in diabetic animals and humans (Glass et al., 1997, Curr. Opin. Cell Biol. 9, 222-232).

In vitro assay

Cotransfection assay

In order to test the ability of compounds of the invention to activate human PPAR-gamma, the following method can be used. CV1 cells (5 10^4 cells/ well of a 96 wells plate) are grown in DMEM supplemented with L-Glutamine (2 mM), penicilline / streptomycin, 10 % Fetal Calf Serum charcoal and dextran treated. 1 ng of GAL4-hPPAR-gamma LBD plasmid is co-transfected with 4 ng of Luciferase reporter plasmid, 8 ng of pCMV-betaGAL as an internal transfection standard and 47 ng of

pBSK as a carrier using Fugene reagent (Roche). After 16 hours, medium is changed to DMEM supplemented with L-Glutamine (2 mM), penicilline / streptomycin, 10 % Delipidated Fetal Calf Serum and cell are treated with increasing dose (1 10^{-10} M to 1 10^{-5} M) of either rosiglitazone or compounds of the invention for 24 hours. Cells are then lysed with 100 µl lysis buffer (40 mM TRIS pH 7.8, 2.14 mM MgCl2, 5.4 mM MgSO4, 0.2 mM EDTA, 66.6 mM DTT) and 50 µl are subject to luciferase assay whereas 30 µl are used for the *betagal* assay. Data are presented in RLU (Relative Light Unit) and EC50 were calculated using Prism software. Similar protocol can be used for testing the activity of compounds of the invention on human PPAR-alpha (using for example GW2433 as reference compound, Brown et al. 1997, J. Chem. Biol., 4,909-18)) and human PPAR-beta (using for example GW1516 as reference compound, Oliver et al. , 2001, Proc. Natl. Acad. Sci., 98, 5306-11).

Mammalian two hybrid

In order to test the ability of compounds of the invention to recruit the co-activator TIF2, the following method can be used. CV1 cells (10^5 cells/ well of a 24 wells plate) are grown in DMEM supplemented with L-Glutamine (2mM), penicilline / streptomycin, 10% Fetal Calf Serum charcoal and dextran treated. 8 ng of GAL4-TIF2 LBD plasmid is co-transfected with 8 ng of VP16-hPPAR gamma LBD, 8 ng of pSG5-RXR alpha, 32 ng of Luciferase reporter plasmid, 32 ng of pCMV-βGAL as an internal transfection standard and 302 ng of pBSK as a carrier using Fugene reagent (Roche). After 16 hours, medium is changed to DMEM supplemented with L-Glutamine (2mM), penicilline / Streptomycin, 10% Delipidated Fetal Calf Serum and cells are treated with increasing dose (1.10 $^{-10}$ M to 1 10 $^{-5}$ M) of either rosiglitazone or compounds of the invention for 24 hours. Cells are then lysed with 100 µl lysis buffer (40mM TRIS pH 7.8, 2.14 mM MgCl2, 5.4 mM MgSO4, 0.2 mM EDTA, 66.6 mM DTT)

and 50 µl are subject to luciferase assay whereas 30 µl are used for betagal assay. Data are presented in RLU (Relative Light Unit) and EC50 were calculated using Prism software.

Adipocyte differentiation

To test the effect of compounds of the invention on adipogenesis, the well described mouse preadipocyte 3T3L1 cell system can be implemented. 3T3L1 cells are grown to confluence at 37°C, 5% CO_2, in a 24 well plate in DMEM supplemented with L-Glutamine (2 mM), penicilline / streptomycin, 10 % Calf Serum. Two days post confluency, cell are changed to DMEM supplemented with L-Glutamine (2 mM), penicilline / streptomycin, 10 % Fetal Calf Serum. Insulin (10 mg/ml) and either rosiglitazone at 1 µM or compounds of the invention at 10 µM, both in DMSO 0.25% final are then added to cells for 3 days. The same treatment is then repeated for an additional 2 days. Finally, cells are grown for another 2 days in DMEM supplemented with L-Glutamine (2 mM), penicilline / streptomycin, 10 % Fetal Calf Serum. Adipogenic effect is then quantified through the measurement of triglyceride content using the Triglyceride GPO Tinder test (SIGMA). Data are expressed as a percent of rosiglitazone effect.

Insulin Stimulated Glucose Uptake (ISGU)

3T3L1 cells are grown to confluence at 37°C, 5% CO_2, in a 48 well plate in DMEM supplemented with L-Glutamine (2 mM), penicilline / streptomycin, 10 % Calf Serum. Two days post confluency, cell are changed to DMEM supplemented with L-Glutamine (2 mM), penicilline / streptomycin, 10 % Fetal Calf Serum (DMEM + 10% FCS), and an hormonal cocktail composed of : Insulin (10 µg/ml), IBMX (500 µM) and Dexamethasone (1 µM) for 3 days. Cells are then treated for an additional 2 days with DMEM + 10% FCS and Insulin (10 µg/ml). Finally, cells are grown for another 2 days in DMEM +10% FCS to complete adipocyte differentiation. Rosiglitazone at 10 µM or compounds

of the invention at 10 µM, both in DMSO 0.25% final are then added everyday to cells for 3 days. Cells are rinsed with serum-free DMEM twice and incubated for 3 hours at 37°C, 5% CO_2. Cells are then washed four times with KRPH buffer (5 mM phosphate, pH 7.4 (NaH_2PO_4-H_2O + Na_2HPO_4-$7H_2O$), 20 mM HEPES pH 7.4, 1 mM $MgSO_4$, 1 mM $CaCl_2$, 136 mM NaCl, 4.7 mM KCl). The buffer is removed and the cells are incubated with or without 100 nM Insulin in KRPH buffer for 20 minuts at 37°C. The buffer is replaced with 0.25 µCi/well of [3H]-2-deoxy-D-Glucose in KRPH buffer supplemented with 25 mM 2-deoxy-D-Glucose with incubation for 5 minuts at room temperature. Supernatant is removed, cells washed four times with cold PBS and lysed with 0.1N NaOH. 400 µl of lysate is neutralized with 40 µl of 1N HCl and added in a scintillation vial with 4 ml of Ready Safe™ (Beckman Coulter). The vials are mixed and counted. Data are expressed both for basal and insulin stimulated glucose uptake as a percent of rosiglitazone effect.

In vivo assay

Hematocrit Assay

Male C57B6J mice aged 8 weeks are treated twice a day by oral gavage in Carboxy Methyl Cellulose 1 % + Tween 80 0,1 % with either vehicle alone, rosiglitazone at 10 mg/kg/day or compounds of the invention at 10 mg/kg/day. On the fifth day of treatment, the hematocrit is quantified by measurement of percentage of Packed Red Cells Volume (PCV) in blood. Data are presented as a percentage of rosiglitazone effect.

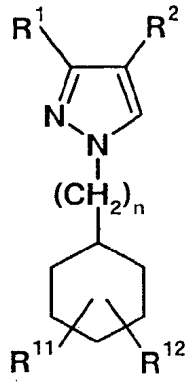
Anti-diabetic activity in *db/db* mouse

Male Diabetic db/db mice aged 8 weeks are treated twice a day for 14 days by oral gavage in Carboxy Methyl Cellulose 1% + Tween 80 0,1 % with either vehicle alone, rosiglitazone at 10 mg/kg/day or compounds of the invention at 10 mg/kg/day. Animals are bleed two days before initiation of the treatment

and then at day 7 and at completion of the experiment (14 days treatment). Plasma biochemical measurements include : total Cholesterol, HDL-Cholesterol, Triglycerides, Glucose, Non Esterified Fatty Acids, Insulin (-2, 7, 14 days) and liver enzymes for toxicity i.e Alkaline Phosphatase and Transaminases (ASAT, ALAT) at completion of the experiment. Additional measurement includes every other day body weight monitoring, food and water intake per cage. Every animal serve as his own control and results are expressed as percent changes.

CLAIMS

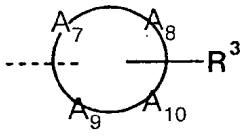
1. A compound of the following general formula (I):



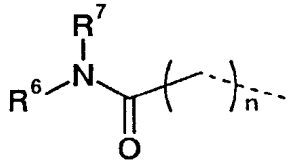
or analogues, derivatives, solvates or salts thereof, wherein :

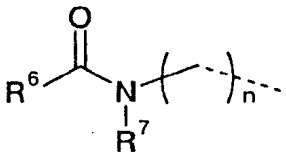
R^1 is a moiety selected in the group consisting of :

(i)

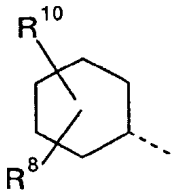


(ii)





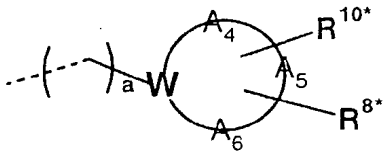
(iii)



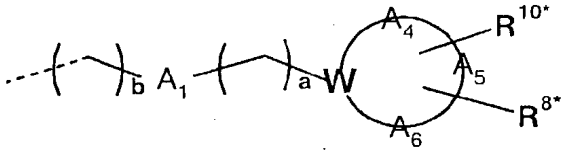
(iv) H, CF_3, $-(CH_2)_n-R^3$ and $-C_{n'}H_{2n'+1}$

R^2 is a moiety selected in the group consisting of :

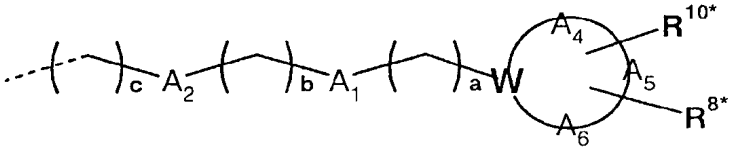
(i)



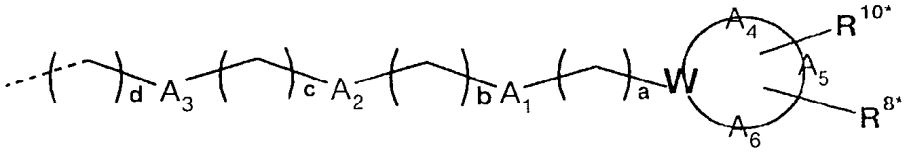
(ii)



(iii)



(iv)



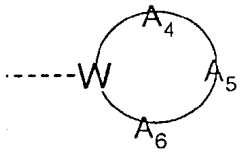
with :

X is a moiety selected in the group consisting of O and S ;

a, **b**, **c** and **d** are, independently from one another, an integer ranging from 0 to 4 ;

A_1, A_2 and A_3 are, independently from one another, a moiety selected in the group consisting of - CO-, -O-, -CH-, $-CH_2-$, $-NR^9-$, and -CHOH- where R^9 is as above mentioned;

the moiety :



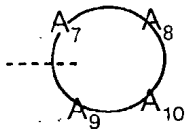
is intended to designate a mono or bi-cyclic carbo or hetero ring which can be unsaturated, or partially or completely saturated, containing 5-10 atoms;

W is an atom selected in the group consisting of C and N ;

$\mathbf{A_4}$, $\mathbf{A_5}$, $\mathbf{A_6}$ are, independently from one another, an atom selected in the group consisting of C, N, O and S ;

$\mathbf{A_7}$, $\mathbf{A_8}$, $\mathbf{A_9}$ and $\mathbf{A_{10}}$ are an atom selected in the group consisting of C, N, S and O ;

the moiety :



is intended to designate :

(ix) a mono carbocyclic ring (i.e. a cyclic carboalkyl, with A_7, A_8, A_9 and A_{10} are C) ;

(x) a mono heterocyclic ring (i.e. a cyclic heteroalkyl, with at least one A_7, A_8, A_9 and/or A_{10} is selected in the group consisting of N, S and O);

(xi) a bi- carbocyclic ring (i.e. a bicyclic carboalkyl with A_7, A_8, A_9 and A_{10} are C);

(xii) a bi- heterocyclic ring (i.e. a bicyclic heteroalkyl with at least one cyclic ring is containing at least one A_7, A_8, A_9 and/or A_{10}

selected in the group consisting of N, S and O);

R^3 is a moiety selected in the group consisting of H, a C_{1-4} alkyl moiety (esp. methyl), $-(CH_2)_n-CONR^{13}R^5$, $-CO_2R^4$, $-COR^4$ (esp. -CO-methyl or $-CONH_2$), $-OR^4$ (esp. -O-methyl), $-(CH_2)_n-CO_2R^4$, $-(CH_2)_n-COR^4$, $-(CH_2)_n-OR^4$, $NR^{13}R^5$, $-(CH_2)_n-NR^{13}R^5$, $-NH-COR^4$, $-(CH_2)_n-NH-COR^4$, -Cl, -F, $-(CH_2)_nCO_2H$, $-O-(CH_2)_nCO_2H$, $(CH_2)_n$-TZD, $-O-(CH_2)_n$-TZD, -CN, $-NO_2$, -OH, $-OCF_3$, $COCF_3$, $-CF_3$, $-N(C_{n'}H_{2n'+1})_2$, $-SO_2-N(R^9)(R^{9*})$, $-NR^9-SO_2CF_3$, and $-NR^9-SO_2-C_{n'}H_{2n'+1}$ (e.g. $-NR^9-SO_2$butyl);

R^4 is a moiety selected in the group consisting of H, $-C_{n'}H_{2n'+1}$ (e.g. C_{1-4} alkyl moiety such as methyl and ethyl), $-(CH_2)_nCO_2H$, $-NH_2$, $-(CH_2)_n$-TZD, -OH, $-N(C_{n'}H_{2n'+1})_2$, $-NR^9-SO_2CF_3$ and $-NR^9-SO_2-C_{n'}H_{2n'+1}$ (e.g. $-NR^9-SO_2$butyl);

R^5 and R^{13} are, independently from one another, a moiety selected in the group consisting of H, a C_{1-4} alkyl moiety (e.g. methyl and ethyl), $-SO_2CF_3$, and $-SO_2-C_{n'}H_{2n'+1}$ (e.g. SO_2butyl);

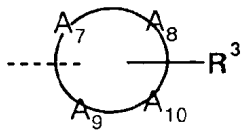
R^6 and R^7 are, independently from one another, a moiety selected in the group consisting of H, an alkyl, more specifically a C_{1-4} alkyl moiety, a C_6 cycloalkyl moiety (e.g. a cyclohexyl or a phenyl moiety), or a C_7 cycloalkyl moiety (e.g. a cycloheptyl or a benzyl moiety), $-SO_2CF_3$, $-SO_2-C_{n'}H_{2n'+1}$ (e.g. $-SO_2$Butyl), a benzyl moiety or phenyl moiety substituted at position 2 and/or 3 and/or 4 with a moiety selected in the group consisting of $-OC_{n'}H_{2n'+1}$, -Cl, -F, $-(CH_2)_nCO_2H$, $-O-(CH_2)_nCO_2H$, $-(CH_2)_n$-TZD, $-O-(CH_2)_n$-TZD, -CN, $-NO_2$, $-C_{n'}H_{2n'+1}$, $-CO-C_{n'}H_{2n'+1}$, $-SO_2-C_{n'}H_{2n'+1}$, $-NR^9-SO_2CF_3$, $-NR^9-SO_2-C_{n'}H_{2n'+1}$ (e.g. $-NR^9-SO_2$butyl), $-OCF_3$, $-COCF_3$, $-CF_3$;

R^8 and R^{8*} are, independently from one another, a moiety selected in the group consisting of H, $-C_{n'}H_{2n'+1}$, a C_6 cycloalkyl moiety (e.g. a cyclohexyl or a phenyl moiety), $-OC_{n'}H_{2n'+1}$, -Cl, -F, $-(CH_2)_nCO_2H$, $-CF_3$, $-OCF_3$, $-COCF_3$, $-O-(CH_2)_nCO_2H$, $-(CH_2)_n$-TZD, $-O-(CH_2)_n$-TZD, $-CH-(CH_2)_n$, $-(CH_2)_n-N(R^9)(R^{9*})$, -CN, $-NO_2$, $-(CH_2)_n-CO-C_{n'}H_{2n'+1}$, $-(CH_2)_n-CO-N(R^9)(R^{9*})$, $-SO_2-N(R^9)(R^{9*})$, $-NR^9-SO_2CF_3$, $-(CH_2)_n$-CO-cycloalkyl (e.g. -CO-cyclohexyl or -CO-phenyl), $-O-(CH_2)_n$- cycloalkyl (e.g. $-O-(CH_2)_n$-cyclohexyl or $-O-(CH_2)_n$-phenyl), $-(CH_2)_n$-cycloalkyl (e.g. $-(CH_2)_n$-cyclohexyl or $-(CH_2)_n$-phenyl), $-NR^9-SO_2-C_{n'}H_{2n'+1}$ (e.g. $-NR^9-SO_2$butyl);

R^9 and R^{9*} are, independently from one another, a moiety selected in the group consisting of H, $-CO-C_{n'}H_{2n'+1}$, $-SO_2-C_{n'}H_{2n'+1}$, and a C_{1-4} alkyl moiety;

R^{10} and R^{10*} are, independently from one another, a moiety selected in the group consisting of H, an alkyl, more specifically a C_{1-4} alkyl moiety, a C_6 cycloalkyl moiety (e.g. a cyclohexyl or a phenyl moiety), or a C_7 cycloalkyl moiety (e.g. a cycloheptyl or a benzyl moiety),-Cl, $-OC_{n'}H_{2n'+1}$, $-CF_3$, $-OCF_3$, $-COCF_3$,-CN, $-NO_2$;

R^{11} and R^{12} is, independently from one another, a moiety selected in the group consisting of H, a C_{1-4} alkyl moiety, $-(CH_2)_n-CONR^{13}R^5$, $-CO_2R^4$, $-COR^4$, $-OR^4$, $-(CH_2)_n-CO_2R^4$, $-(CH_2)_n-COR^4$, $-(CH_2)_n-OR^4$, $-NR^{13}R^5$, $-(CH_2)_n-NR^{13}R^5$, $-NH-COR^4$, $-(CH_2)_n-NH-COR^4$, $-OC_{n'}H_{2n'+1}$, -Cl, -F, $-(CH_2)_nCO_2H$, $-O-(CH_2)_nCO_2H$, $-(CH_2)_n$-TZD, $-O-(CH_2)_n$-TZD, -CN, $-NO_2$, -OH, $-OCF_3$, $-COCF_3$, $-CF_3$, $-N(C_{n'}H_{2n'+1})_2$, $-SO_2-N(R^9)(R^{9*})$, $-NR^9-SO_2CF_3$, $-NR^9-SO_2-C_{n'}H_{2n'+1}$ (e.g. $-NR^9-SO_2$butyl), and :



;

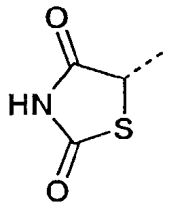
and

with in all the above :

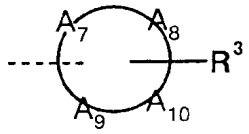
n is, independently from one another, an integer ranging from 0 to 6,

n' is, independently from one another, an integer ranging from 1 to 4, preferably from 1 to 3 and preferably from 1 to 2 ;

and TZD is :



2. The compound of claim 1 wherein the R^1 moiety :



is intended to designate :

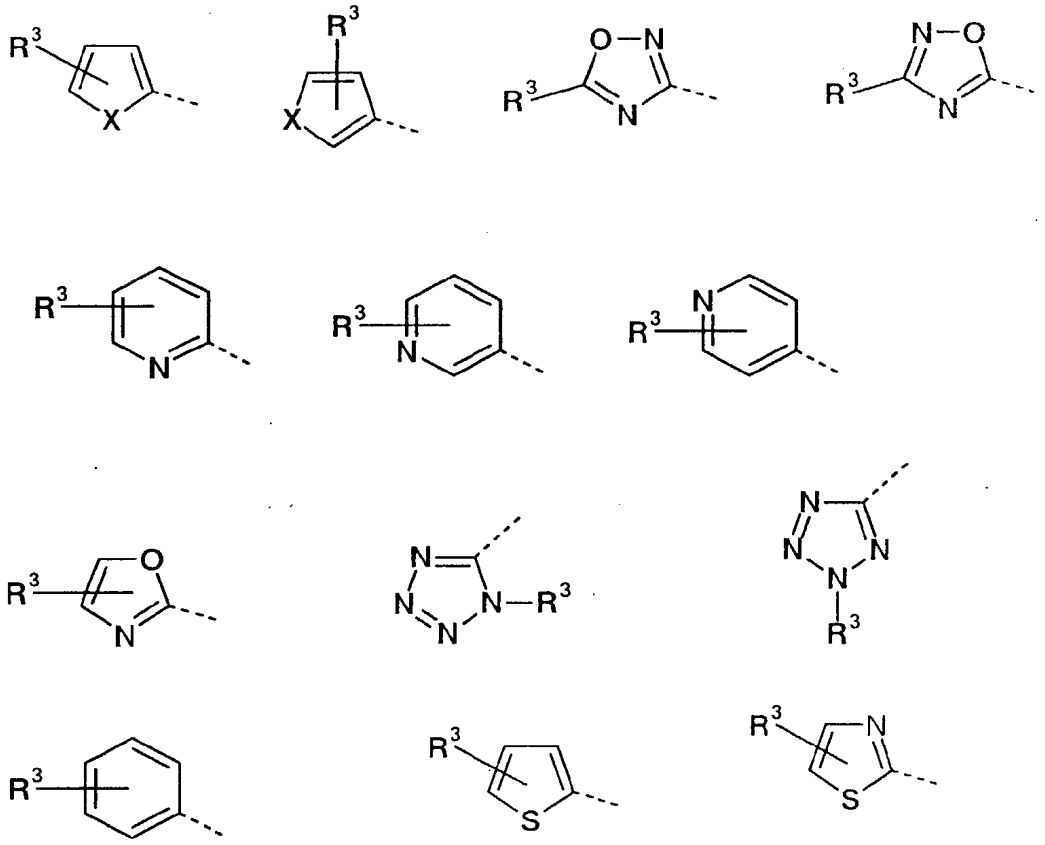
(i) a R^3 substituted mono carbocyclic ring (i.e. a cyclic carboalkyl, with A_7, A_8, A_9 and A_{10} are C) ;

(ii) a R^3 substituted mono heterocyclic ring (i.e. a cyclic heteroalkyl, with at least one A_7, A_8, A_9 and/or A_{10} is selected in the group consisting of N, S and O);

(iii) a R^3 substituted bi- carbocyclic ring (i.e. a bicyclic carboalkyl with A_7, A_8, A_9 and A_{10} are C);

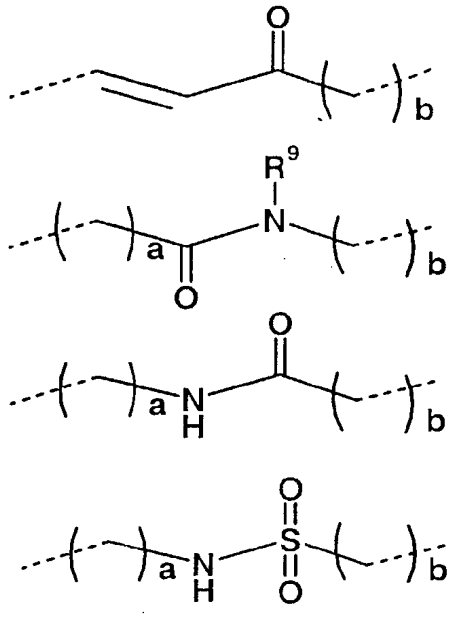
(iv) a R^3 substituted bi- heterocyclic ring (i.e. a bicyclic heteroalkyl with at least one cyclic ring is containing at least one A_7, A_8, A_9 and/or A_{10} selected in the group consisting of N, S and O).

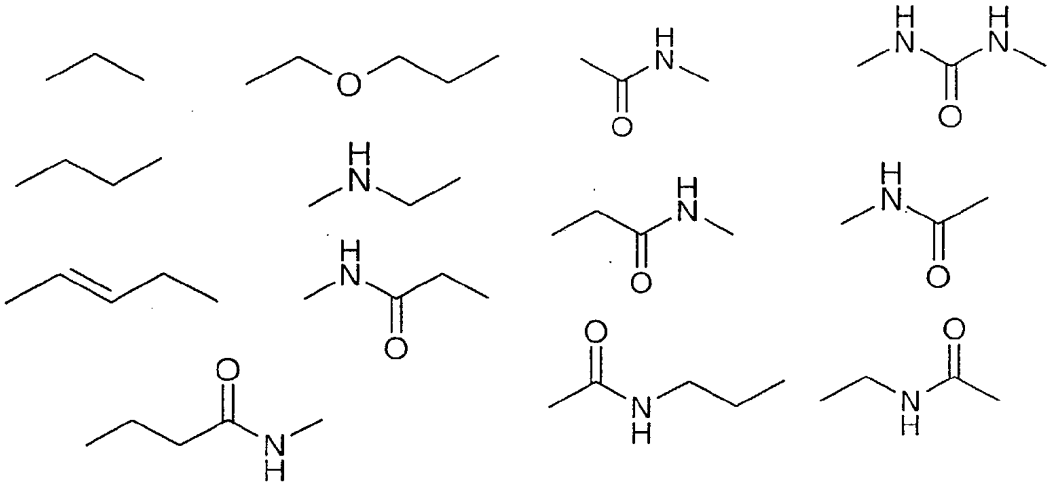
3. The compound of claim 1 or 2 wherein the R^1 moiety is selected in the group consisting of :



with X is a moiety selected in the group consisting of O, N and S.

4. The compound of claims 1 to 3 wherein the linker in structure R^2 is selected in the group consisting in :





5. A compound of claims 1 to 4 selected in the group consisting in :

2-(1-Methyl-1H-indol-3-yl)-N-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-acetamide (CRX000339);

Benzo[1,3]dioxole-4-carboxylic acid (1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-amide (CRX000329);

2-Naphthalen-1-yl-N-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-acetamide (CRX000330);

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid isoxazol-3-ylamide (CRX000238);

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (2,5-dimethyl-2H-pyrazol-3-yl)-amide (CRX000376);

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (3-methyl-isothiazol-5-yl)-amide (CRX000241);

1-Phenyl-4-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethyl)-piperazine (CRX000404) ;

6-Methoxy-2-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethylene)-indan-1-one (CRX000548);

N-(1-Phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethyl)-nicotinamide (CRX000538) ;

2-(1-Phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethyl)-isoindole-1,3-dione (CRX000466) ;

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (2-ethyl-2H-pyrazol-3-yl)-amide (CRX000148);

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (4-methoxy-6-methyl-pyrimidin-2-yl)-amide (CRX000260);

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (4-oxo-4,5-dihydro-thiazol-2-yl)-amide (CRX000244);

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (1H-[1,2,4]triazol-3-yl)-amide (CRX000354);

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (thiophen-2-ylmethyl)-amide (CRX000243);

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (5-methyl-furan-2-ylmethyl)-amide (CRX000265);

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (furan-2-ylmethyl)-amide (CRX000221);

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (3,4-dimethyl-isoxazol-5-yl)-amide (CRX000266);

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (1H-tetrazol-5-yl)-amide (CRX000177);

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (pyridin-4-ylmethyl)-amide (CRX000194);

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (pyridin-3-ylmethyl)-amide (CRX000267);

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (pyridin-2-ylmethyl)-amide (CRX000242);

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid pyridin-2-ylamide (CRX000355);

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid pyridin-3-ylamide (CRX000356);

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid pyridin-4-ylamide (CRX000187).

5-Methoxy-2-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethylene)-indan-1-one (CRX000405) ;

5-Methoxy-2-(1-phenyl-3-pyridin-3-yl-1H-pyrazol-4-ylmethylene)-indan-1-one (CRX000445)

6-Methoxy-2-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethyl)-benzo[d]isoxazol-3-one ;

5-Methoxy-3-methyl-2-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethyl)-inden-1-one;

5-Methoxy-2-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethyl)-inden-1-one ;

5-Methoxy-2-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethyl)-indan-1-one (CRX000440);

6-Methoxy-2-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethylene)-3,4-dihydro-2H-naphthalen-1-one (CRX000366) ;

2-(1-Phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethyl)-isoindole-1,3-dione (CRX000466) ;

2-(1-Phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethyl)-2,3-dihydro-isoindol-1-one ;

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (1-benzyl-piperidin-4-yl)-amide (CRX000153) ;

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (2-morpholin-4-yl-ethyl)-amide (CRX000154) ;

1-[4-(1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carbonyl)-piperazin-1-yl]-ethanone (CRX000161) ;

(3,4-Dihydro-2H-quinolin-1-yl)-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-methanone (CRX000162) ;

(1-Phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-piperidin-1-yl-methanone (CRX000164) ;

Morpholin-4-yl-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-methanone (CRX000166) ;

4-Methyl-piperidin-1-yl)-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-methanone (CRX000170) ;

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (1H-indazol-5-yl)-amide (CRX000175) ;

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (naphthalen-1-ylmethyl)-amide (CRX000193) ;

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)-amide (CRX000202) ;

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid naphthalen-2-ylamide (CRX000204) ;

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid indan-5-ylamide (CRX000219) ;

(4-Phenyl-piperazin-1-yl)-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-methanone (CRX000222) ;

1-{4-[4-(1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carbonyl)-piperazin-1-yl]-phenyl}-ethanone (CRX000223) ;

(1-Phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-(4-pyridin-2-yl-piperazin-1-yl)-methanone (CRX000224) ;

(3,4-Dihydro-1H-isoquinolin-2-yl)-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-methanone (CRX000225) ;

(4-Benzyl-piperazin-1-yl)-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-methanone (CRX000226) ;

[4-(4-Methoxy-phenyl)-piperazin-1-yl]-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-methanone (CRX000227) ;

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (1H-indol-5-yl)-amide (CRX000258) ;

4-(4-Methoxy-phenyl)-piperazin-1-yl]-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-methanone (CRX000269) ;

4-(1-Phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethyl)-morpholine (CRX000299) ;

4-Methyl-1-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethyl)-piperidine (CRX000300) ;

(4-Benzyl-piperidin-1-yl)-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-methanone (CRX000307) ;

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (2-methyl-1,3-dioxo-2,3-dihydro-1H-isoindol-5-l)-amide (CRX000309) ;

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid furan-2-ylmethyl-methyl-amide (CRX000311) ;

N-(1-Phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-nicotinamide (CRX000328) ;

N-(1-Phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-isonicotinamide (CRX000333) ;

Pyridine-2-carboxylic acid (1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-amide (CRX000334) ;

1-[4-(1-Phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethyl)-piperazin-1-yl]-ethanone (CRX000341) ;

1-(1-Phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethyl)-piperidine (CRX000343) ;

1-Benzyl-4-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethyl)-piperazine (CRX000352) ;

1-Methyl-1H-indole-3-carboxylic acid (1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-amide (CRX000377) ;

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid methyl-pyridin-2-yl-amide (CRX000381) ;

Thiophene-2-carboxylic acid (1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-amide (CRX000393) ;

1-Acetyl-piperidine-4-carboxylic acid (1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-amide (CRX000400) ;

1-Benzo[1,3]dioxol-5-ylmethyl-4-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethyl)-piperazine (CRX000403) ;

1-(4-Isopropyl-phenyl)-4-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethyl)-piperazine (CRX000438) ;

6-Methoxy-2-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethyl)-3,4-dihydro-2H-naphthalen-1-one (CRX000439) ;

2-(1-Phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethylene)-indan-1-one (CRX000470) ;

3-(4-Methoxy-phenyl)-5-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-[1,2,4]oxadiazole (CRX000459);

3-(4-Methoxy-benzyl)-5-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-[1,2,4]oxadiazole (CRX000513) ;

1-Phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethyl-ammonium (CRX000514) ;

N-(1-Phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethyl)-isonicotinamide (CRX000584) ;

Pyridine-2-carboxylic acid (1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethyl)-amide (CRX000575) ;

2-(1-Phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethyl)-2,3-dihydro-isoindol-1-one (CRX000602).

According to further particular embodiments, the compound of the invention is selected in the group consisting in :

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid butylamide (CRX000191) ;

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (2-acetylamino-ethyl)-amide (CRX000217) ;

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid ethylamide (CRX000239) ;

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (2-oxo-propyl)-amide (CRX000240) ;

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid [4-(2-oxo-propylamino)-butyl]-amide (CRX000257) ;

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (2-methoxy-ethyl)-amide (CRX000262) ;

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid diethylamide (CRX000268) ;

Diethyl-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethyl)-amine (CRX000279) ;

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (3-dimethylamino-propyl)-methyl-amide (CRX000298) ;

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid dibenzylamide (CRX000306) ;

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid dimethylamide (CRX000310) ;

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid methyl-propyl-amide (CRX000312) ;

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid (3-dimethylamino-propyl)-methyl-amide (CRX000340) ;

Methyl-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-ylmethyl)-propyl-amine (CRX000353) ;

1-Phenyl-3-thiophen-2-yl-1H-pyrazole-4-carboxylic acid diisopropylamide (CRX000397) ;

2-Acetylamino-N-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-acetamide (CRX000399) ;

5-Methyl-2-phenyl-4-[3-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-allyl]-oxazole (CRX000783).

6. A PPAR-gamma agonist having the structure of compound of claims 1 to 5.

7. A composition comprising at least one compound of claims 1 to 6.

8. A method for treating obesity, said method comprising administering to a patient in need of such treatment an amount of at least one compound or a composition of claims 1-7.

9. A method for treating diabetes, said method comprising administering to a patient in need of such treatment an amount of at least one compound or a composition of claims 1-7.

10. A method for modulating insulin-sensitivity and blood glucose levels in a patient, said method comprising

administering to a patient in need of such treatment an amount of compound or a composition of claims 1-7.

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